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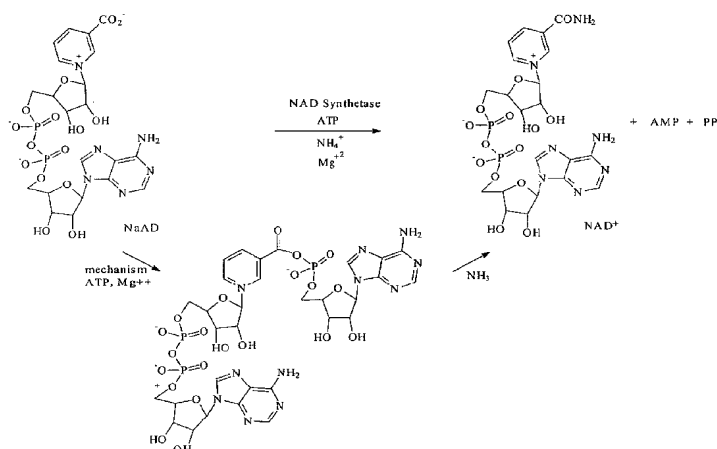
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(54) Title: NAD SYNTHETASE INHIBITORS AND USES THEREOF



(57) **Abstract:** Disclosed are compounds that inhibit the microbial NAD synthetase enzyme. For example, disclosed are compounds of the formula Ar₁-X-Ar₂-Y-L-Z-Q, wherein Q is Q₁Ar₃ or Ar₃Q₁; Ar₁, Ar₂, and Ar₃ are independently aryl or heteroaryl, optionally substituted with one or more substituents; X, Y, and Z are independently selected from the group consisting of a covalent bond or groups containing one or more of C, H, N, O, S atoms; L is a linker and Q₁ is an alkylenyl, alkylenyl carbonyloxy alkyl, or alkylenyl carbonylamino alkyl group, optionally having a substituent; a covalent bond; a group containing amidine or guanidine function wherein the amidine or guanidine may be optionally N-substituted with an alkyl; or a zwitterion; or a pharmaceutically acceptable salt thereof. Also disclosed are methods which involve the use of the compounds of the present invention, for example, in treating or preventing a microbial infection in a mammal or plant, killing a prokaryote or decreasing prokaryotic growth, disinfecting a material or environment contaminated by a microbe, increasing food animal production, controlling harm to plants by a pest or insect and combating agroterrorism. Examples of microbes affected by the compounds of the present invention are bacteria and fungi.



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NAD SYNTHETASE INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation-in-part of co-pending U.S. patent application No. 09/617,258, filed July 14, 2000, which is a continuation of International Application No. PCT/US99/14839, filed June 30, 1999, which in turn is a continuation-in-part of International Application No. PCT/US99/00810, filed January 14, 1999, and claims the benefit of U.S. provisional patent application Nos. 60/097,880, filed August 25, 1998 and 60/071,399, filed January 14, 1998. The present application is also a continuation-in-part of co-pending U.S. patent application No. 09/606,256, filed June 29, 2000, which claims the benefit of U.S. provisional patent application No. 60/141,436, filed June 29, 1999, and a continuation-in-part of PCT/US00/18029, filed June 29, 2000. The present application is also a continuation-in-part of International Application No. PCT/US01/22203, filed July 13, 2001, which claims the benefit of U.S. provisional patent application No. 60/218,405, filed July 14, 2000. The disclosures of all of the related applications mentioned herein are incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED
RESEARCH AND DEVELOPMENT

Some research that contributed to the invention herein was supported, in part, by a grant from the Government of the United States of America, Defense Advanced Research Projects Agency. The Government may have certain rights in this invention.

FIELD OF THE INVENTION

The present invention in general relates to antimicrobial agents, and in particular, to inhibitors of the nicotinamide adenine dinucleotide (NAD) synthetase enzyme of microbes such as bacteria and fungi. The present invention also relates to the various uses of these antimicrobial agents, including in a method of treating or preventing a microbial infection in a mammal, in a method of treating the environment against microbial contamination, in agriculture, e.g., in raising foodcrops and food animals, in medicine, e.g., to disinfect, sterilize, or decontaminate equipment, devices, rooms, and/or people, and in combating bioterrorism, e.g., agroterrorism.

BACKGROUND OF THE INVENTION

Drug-resistant infectious bacteria, that is, bacteria that are not killed or inhibited by existing antibacterial and antimicrobial compounds, have become an alarmingly serious
5 worldwide health problem. Rubenstein, *Science*, **264**, 360 (1994). It is believed that a number of bacterial infections may soon be untreatable unless alternative drug treatments are identified.

Antimicrobial or antibacterial resistance has been recognized since the introduction of penicillin nearly 50 years ago. At that time, penicillin-resistant infections caused by
10 *Staphylococcus aureus* rapidly appeared. Today, hospitals worldwide are facing challenges from the rapid emergence and dissemination of microbes resistant to one or more antimicrobial and antibacterial agents commonly in use today. Several strains of antibiotic-resistant bacteria are now emerging and are becoming a threat to human and animal populations, including those summarized below:

15 Strains of *Staphylococcus aureus* resistant to methicillin and other antibiotics are endemic in hospitals. Infection with methicillin-resistant *S. aureus* (MRSA) strains may also be increasing in non-hospital settings. Vancomycin is the only effective treatment for MRSA infections. A particularly troubling observation is that *S. aureus* strains with reduced susceptibility to vancomycin have emerged recently in Japan and the United States.
20 The emergence of vancomycin-resistant strains would present a serious problem for physicians and patients.

Increasing reliance on vancomycin has led to the emergence of vancomycin-resistant *enterococci* (VRE), bacteria that infect wounds, the urinary tract and other sites. Until 1989, such resistance had not been reported in U.S. hospitals. By 1993, however,
25 more than 10 percent of hospital-acquired *enterococci* infections reported to the Centers for Disease Control ("CDC") were resistant.

Streptococcus pneumoniae causes thousands of cases of meningitis and pneumonia, as well as 7 million cases of ear infection in the United States each year. Currently, about 30 percent of *S. pneumoniae* isolates are resistant to penicillin, the primary drug used to
30 treat this infection. Many penicillin-resistant strains are also resistant to other antimicrobial or antibacterial drugs.

Strains of multi-drug resistant tuberculosis (MDR-TB) have emerged over the last

decade and pose a particular threat to people infected with HIV. Drug-resistant strains are as contagious as those that are susceptible to drugs. MDR-TB is more difficult and vastly more expensive to treat, and patients may remain infectious longer due to inadequate treatment. Multi-drug resistant strains of *Mycobacterium tuberculosis* have also emerged in
5 several countries, including the U.S.

Diarrheal diseases cause almost 3 million deaths a year, mostly in developing countries, where resistant strains of highly pathogenic bacteria such as *Shigella dysenteriae*, *Campylobacter*, *Vibrio cholerae*, *Escherichia coli* and *Salmonella* are emerging. Furthermore, recent outbreaks of *Salmonella* food poisoning have occurred in the United
10 States. A potentially dangerous "superbug" known as *Salmonella typhimurium*, resistant to ampicillin, sulfa, streptomycin, tetracycline and chloramphenicol, has caused illness in Europe, Canada and the United States.

In addition to its adverse effect on public health, antimicrobial resistance contributes to higher health care costs. Treating antibiotic resistant infections often requires the use of
15 more expensive or more toxic drugs and can result in longer hospital stays for infected patients. The Institute of Medicine, a part of the National Academy of Sciences, has estimated that the annual cost of treating antibiotic resistant infections in the United States may be as high as \$30 billion.

In addition, the use of antibiotics in food animal feeds and the extent to which such
20 use contributes to the development of drug resistance have been under recent discussion, see, e.g., C. Marwick, "Animal Feed Antibiotic Use Raises Drug Resistance Fear," *Journal of the American Medical Association*, 282(2):120-2, July 14, 1999, and T. R. Shryock, "Relationship between usage of antibiotics in food-producing animals and the appearance of antibiotic resistant bacteria," *International Journal of Antimicrobial Agents*, 12(4):275-8,
25 Aug 1999. The use of antibiotics as well as biocides can lead to antibiotic or drug-resistant organisms, see, e.g., A. D. Russel, "Mechanisms of bacterial resistance to antibiotics and biocides," *Progress in Medicinal Chemistry*, 35:133-97, 1998.

Further, spore-forming bacteria can be lethal. For example, *Bacillus anthracis* causes the deadly disease, anthrax. There exists an uncertainty relating to the efficacy of
30 currently available vaccines against *B. anthracis*. Further, there is a likelihood that terrorists could employ antibiotic-resistant strains, e.g., engineered strains that are not recognized by *B. anthracis* antibodies or common bacteria engineered to carry the virulence

gene (see, e.g., T. C. Dixon et al., "Anthrax," *New England Journal of Medicine*, 341 (11), 815-826, Sept. 1999). The foregoing shows that there exists a need for a novel treatment against spore-forming bacteria, particularly *B. anthracis* or bacteria carrying the virulence gene of *B. anthracis*.

5 Further, the incidence of serious fungal infections, either systemic or topical, continues to increase for plants, animals, and humans. Fungi are plant-like eukaryotes that grow in colonies of single cells, called yeasts, or in filamentous multicellular aggregates, called molds. While many fungi are common in the environment and not harmful to plants or mammals, some are parasites of terrestrial plants and others can produce disease in
10 humans and animals. When present in humans, mycotic (fungal) diseases can include contagious skin and hair infections, noncontagious systemic infections, and noncontagious foodborne toxemias. The incidence of such infections is not insignificant; in the U.S. approximately 10% of the population suffers from contagious skin and hair infections. While few healthy persons develop life-threatening systemic fungal infections,
15 immunocompromised individuals, such as found in pregnancy, congenital thymic defects, or acquired immune deficiency syndrome (AIDS), can become seriously ill. This is further illustrated by the fact that fungal infections have become a major cause of death in organ transplant recipients and cancer patients.

Numerous antifungal agents have been developed for topical use against
20 nonsystemic fungal infections. However, the treatment of systemic fungal infections, particularly in immunocompromised hosts, continues to be a major objective in infectious disease chemotherapy. The organisms most commonly implicated in systemic infections include *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus* spp., although there are a number of emerging pathogens. The major classes of systemic drugs in use currently are
25 the polyenes (e.g., amphotericin B) and the azoles (e.g., fluconazole). While somewhat effective in otherwise healthy patients, these agents are inadequate in severely immunocompromised individuals. Furthermore, drug resistance has become a serious problem, rendering these antifungal agents ineffective in some individuals.

One reason for the limited number of systemic antifungal agents relates to the fact
30 that, unlike bacteria, which are prokaryotes, yeast and molds are eukaryotes. Thus the biochemical make-up of yeast and molds more closely resembles eukaryotic human and animal cells. In general, this has made it difficult to develop antifungal drugs which

selectively target in yeast or mold an essential enzyme or biochemical pathway that has a close analog in humans and animals.

In addition, in view of the risks such as toxicity or carcinogenicity associated with many common pesticides, fungicides, or bactericides, new approaches are needed to control pests, or insects in the environment, as well as microbial diseases in plants and food crops, see, e.g., D. W. Wong and G. H. Robertson, "Combinatorial chemistry and its applications in agriculture and food," *Advances in Experimental Medicine & Biology*, 464:91-105, 1999, and S. H. Zahm and M. H. Ward, "Pesticides and childhood cancer," *Environmental Health Perspectives*, 106, Suppl. 3:893-908, June 1998.

Bioterrorism, especially agricultural bioterrorism (or agroterrorism), is presently of great concern in this country as well as in many countries throughout the world. See, e.g., Joseph W. Foxell, Jr., "Current Trends in Agroterrorism (Antilivestock, Anticrop, and Antisoil Bioagricultural Terrorism) and Their Potential Impact on Food Security", in *Studies in Conflict & Terrorism*, 24, 107-129 (2001); Mark Wheelis, "Agricultural Biowarfare and Bioterrorism - An Analytical Framework and Recommendations for the Fifth BTWC Review Conference", *14th Workshop of the Pugwash Study Group on the Implementation of the Chemical Biological Weapons Conventions*, Geneva, Switzerland, November 2000; Radford G. David, "Agricultural Bioterrorism - New Frontiers" in *Biowarfare*, October 2001; Robert P. Kadlec, Chapter 10, *Biological Weapons for Waging Economic Warfare, Battle of the Future, 21st Century Warfare Issues*, Aerospace Power Chronicles; Senator Kay Bailey Hutchison, S. 1563, *The Agricultural Bioterrorism Countermeasures Act of 2001*, Senate Floor Speech, October 17, 2001, page S. 10796.

Given the above, there exists a need to develop novel antimicrobial agents, especially those which act by different mechanisms than those agents in use currently.

There exists a need to develop antibacterial agents that preferentially attack microorganisms and kill or deactivate the harmful organism without causing any attendant undesirable side effects in a human or animal patient.

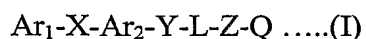
There also exists a need for methods of treating or preventing microbial infection, methods for treating an environment, methods for treating food crops and animals, methods for decontaminating objects, and/or developing countermeasures against bioterrorism, particularly agrobioterrorism.

The advantages of the present invention as well as inventive features will be apparent from the description below.

BRIEF SUMMARY OF THE INVENTION

5 The present invention ameliorates some of the disadvantages of previously known antimicrobial agents. The present invention provides antimicrobial agents comprising two aryl moieties linked by a suitable linker, and the antimicrobial agents inhibit the NAD synthetase enzyme of a microbe.

10 In accordance with an embodiment, the present invention provides a compound of the formula (I):



wherein Q is Q_1Ar_3 or Ar_3Q_1 ;

Ar_1 , Ar_2 , and Ar_3 are independently aryl or heteroaryl, optionally substituted with one or more substituents; X, Y, and Z are independently selected from the group consisting of a
15 covalent bond or groups containing one or more of C, H, N, O, S atoms; L is a linker and

Q_1 is an alkylene, alkylene carbonyloxy alkyl, or alkylene carbonylamino alkyl group, optionally having a substituent; a covalent bond; a group containing amidine or guanidine function wherein the amidine or guanidine may be optionally N-substituted with an alkyl; or a zwitterion;

20 or a pharmaceutically acceptable salt thereof.

The present invention further provides a compound of the formula $\text{A-B-(CH}_2)_n\text{-O-CO-CH}_2\text{-Ph (NMe}_3)^+\text{I}^-$, wherein A is a phenyl or indole, optionally substituted with a benzyloxy group; B is a covalent bond or oxygen atom; n is 1-15; and I is a pharmaceutically acceptable anion.

25 Further, the invention provides a method of treating or preventing a microbial infection in a mammal comprising administering to the mammal a treatment effective or treatment preventive amount of a microbial NAD synthetase enzyme inhibitor compound. Still further, a method is provided of killing a prokaryote with an amount of prokaryotic NAD synthetase enzyme inhibitor to reduce or eliminate the production of NAD whereby
30 the prokaryote is killed. Moreover, a method is provided of decreasing prokaryotic growth, comprising contacting the prokaryote with an amount of prokaryotic NAD synthetase enzyme inhibitor effective to reduce or eliminate the production of NAD whereby

prokaryotic growth is decreased. Further provided is a disinfecting composition comprising a microbial NAD synthetase enzyme inhibitor. Still further, the invention provides a method of disinfecting a material contaminated by a microbe, comprising contacting a contaminated material with a microbial NAD synthetase enzyme inhibitor compound in an amount sufficient to kill or deactivate the microbe. The present invention provides a method for treating or preventing a microbial infection in a mammal comprising administering to the mammal an effective amount of a compound that inhibits the enzymatic activity of the microbial NAD synthetase.

The present invention, in an embodiment, is based in part on the discovery that NAD synthetase inhibitors are highly effective in inhibiting the growth of a fungus such as yeast, yet exhibit only moderate toxicity in animals. Thus, the present invention includes the use of NAD synthetase inhibitors as antifungal agents for preventing or controlling fungal infections such as parasitic yeast and mold infections in plants, and for the prophylactic or therapeutic treatment, topically and systemically, of fungal infections in humans and animals. The present invention provides a method of killing a fungus with an amount of NAD synthetase enzyme inhibitor to reduce or eliminate the production of NAD whereby the fungus is killed. The present invention also provides a method of decreasing fungus growth, comprising contacting the yeast with an amount of a NAD synthetase enzyme inhibitor effective to reduce or eliminate the production of NAD whereby fungus growth is decreased.

The present invention also provides a method for increasing production of food animals comprising administering to the food animal an effective amount of at least one inhibitor of NAD synthetase of a microbe capable of infecting the food animal. The present invention further provides a method for the treatment or prevention of infection by a spore-forming bacterium in an animal comprising treating an environment of the animal with an effective amount of at least one inhibitor of NAD synthetase of the spore-forming bacterium.

The present invention further provides a method for killing the vegetative cell of a spore-forming bacterium in an environment comprising treating the environment with an effective amount of at least one inhibitor of NAD synthetase of the bacterium.

The present invention also provides a method for treating a fungal or bacterial disease in a plant comprising treating the plant or the environment of the plant with an

effective amount of at least one inhibitor of NAD synthetase of the fungus or bacterium. The present invention further provides a method for treating or preventing harm to a plant due to a pest comprising contacting the plant, or an environment thereof, with a pesticidal effective amount of a NAD synthetase enzyme inhibitor of the pest.

5 The present invention further provides a pharmaceutical composition comprising a compound as described above and a pharmaceutically acceptable carrier. The present invention further provides a method for treating or preventing a microbial infection in a mammal comprising administering to said mammal an effective amount of a compound that binds to the interface of the NAD synthetase enzyme dimer of the microbe.

10 The present invention further provides a method for combating agroterrorism involving an infective agent on an object comprising treating the object with an amount of a compound effective to inhibit the NAD synthetase of the infective agent.

BRIEF DESCRIPTION OF THE DRAWINGS

15 Fig. 1 depicts a reaction scheme wherein the NAD synthetase enzyme catalyzes the final step in the biosynthesis of NAD.

Fig. 2 schematically illustrates catalytic sites on a bacterial NAD synthetase enzyme.

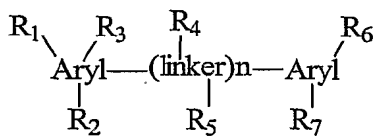
Fig. 3 schematically illustrates the blocking of catalytic sites of a bacterial NAD synthetase enzyme.

20

SPECIFIC DESCRIPTION OF THE INVENTION

The present invention provides a microbial NAD synthetase enzyme inhibitor, having the formula 1:

25



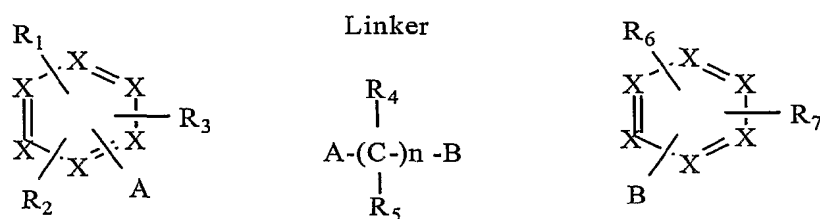
(formula 1)

30 wherein n is an integer of from 1 to 12, R₁-R₇ each, independently, is H, an unsubstituted or a substituted cyclic or aliphatic group, a branched or unbranched group, wherein the linker is a cyclic or aliphatic, branched or an unbranched alkyl, alkenyl, or an alkynyl group and wherein the linker may also contain heteroatoms.

R_1 - R_7 may also be one of the following groups: H, alkyl, alkenyl, alkynyl, or an aryl. R_1 - R_7 , may further be a hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen or a common derivatives of these groups. Note that n may also be an integer of from 3 to 10, more preferably 5 to 9 and, still more preferably 6 to 9. The

5 “aryl,” moieties may be the same or different.

As an example, the present invention provides a microbial NAD synthetase enzyme inhibitor, having formula 2:



(formula 2)

wherein X is a C, N, O or S within a monocyclic or bicyclic moiety, A and B represent the respective sites of attachment for the linker, n is an integer of from 1 to 12, R_1 - R_7 each, independently, is an H, an unsubstituted or a substituted cyclic group, or an aliphatic group, or a branched or an unbranched group, wherein the linker is a saturated or unsaturated

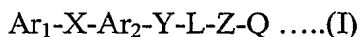
15 cyclic group or an aliphatic branched or unbranched alkyl, alkenyl or alkynyl group, and wherein the linker may also contain heteroatoms.

R_1 - R_7 may also be one of the following groups: H, alkyl, alkenyl, alkynyl, or an aryl group. R_1 - R_7 may also be a hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, sulfonate, or halogen or the common derivatives of these groups. One

20 of skill in the art would know what moieties are considered to constitute derivatives of these groups. In further embodiments, n may also be an integer of from 3 to 10, more preferable 5 to 9 and, still more preferably 6 to 9.

In an embodiments, the linker has the formula A-(C, Heteroatom) n -B. For example, the linker may be an amide, ester, ether, or combinations thereof.

The present invention, in an embodiment, provides a compound of formula (I):



wherein Q is Q_1Ar_3 or Ar_3Q_1 ;

Ar_1 , Ar_2 , and Ar_3 are independently aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and heterocyclyl; optionally, a ring nitrogen atom of heteroaryl Ar_1 , Ar_2 , or Ar_3 may be quaternized;

X, Y, and Z are independently selected from the group consisting of a covalent bond, $(\text{CH}_2)_m\text{O}$, $\text{O}(\text{CH}_2)_m$, $(\text{CH}_2\text{O})_m$, $(\text{OCH}_2)_m$, $(\text{CH}_2\text{CH}_2\text{O})_m$, $(\text{OCH}_2\text{CH}_2)_m$, $\text{C}(=\text{O})\text{O}$, $\text{OC}(=\text{O})$, $\text{OC}(=\text{O})\text{O}$, $(\text{CH}_2)_m\text{S}$, $\text{S}(\text{CH}_2)_m$, $(\text{CH}_2\text{S})_m$, $(\text{SCH}_2)_m$, NH , NR , $^+\text{NR}_2$, $\text{C}(=\text{O})\text{NH}$, $\text{C}(=\text{O})\text{NR}$, $\text{NHC}(=\text{O})$, $\text{NRC}(=\text{O})$, $\text{CH}(\text{OH})$, and $\text{CH}(\text{OR})$, wherein R is C₁-C₆ alkyl and m is 0-5;

L is $\{(\text{CR}_1\text{R}_2)_q\text{-(W)}_t\text{-(CR}_3\text{R}_4)_r\}_p$, wherein R₁-R₄ are independently H, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, azido, hydroxy, aldehyde, C₁-C₆ acetal, C₁-C₆ ketal, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, sulfonamido, C₁-C₆ alkylcarbonylamino, or heterocyclyl; W is a moiety selected from the group consisting of alicyclic ring, aromatic ring, heterocyclic ring, combinations of alicyclic, heterocyclic, and/or aromatic rings, C₂-C₆ alkenyl, dienyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₂-C₆ alkenyloxy, C₂-C₆ alkynyloxy, anhydrido, enol, ketene, amino, imino, hydrazinyl, epoxy, episulfide, amido, amine oxide, urea, urethane, ester, thioester, carbonate, carbonyl, thiocarbonyl, sulfonyl, diazo, sulfonamido, ether oxygen, ether sulfur, thionyl, silyl, peroxide, lactam, lactone, phenylene, monosaccharide, di-, tri-, and higher polysaccharides, nucleic acid, amino acid, phosphonyl, phosphoryl, and combinations thereof; q, r, and t are

independently 0-20; q, r, and t are not simultaneously 0; and p is 1-6; L, optionally, further including O, N, or S; and

Q₁ is (i) a C₁-C₆ alkylenyl, C₁-C₆ alkylenyl carbonyloxy C₁-C₆ alkyl, or C₁-C₆ alkylenyl carbonylamino C₁-C₆ alkyl group, optionally having a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, C₁-C₆ haloalkylamino, C₁-C₆ haloalkyl C₁-C₆ alkyl amino, C₁-C₆ hydroxyalkylamino, C₁-C₆ hydroxyalkyl C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, and heterocyclic containing a nitrogen atom which may be optionally quaternized, (ii) a C₂-C₆ alkylenyl; (iii) methylenyl with the proviso that Z is other than covalent bond or O(C=O) when Q is Q₁Ar₃ wherein Ar₃ is a phenyl *para* substituted with amino, methylamino, dimethylamino, or trimethylamino or Ar₃ is a pyridyl or N-methyl pyridyl; (iv) a covalent bond with the proviso that when Ar₃ is pyridyl, N-methyl pyridyl, or phenyl *para* substituted with trimethylaminomethyl group, Z is other than a covalent bond or O(C=O); (v) a group containing amidine or guanidine function wherein the amidine or guanidine may be optionally N-substituted with a C₁-C₆ alkyl; or (vi) a zwitterion;

or a pharmaceutically acceptable salt thereof.

The aryl of Ar₁, Ar₂, and Ar₃ includes 1-3 aromatic rings, for example, phenyl, naphthyl, or anthracenyl, preferably phenyl. The heteroaryl of Ar₁, Ar₂, and Ar₃ include 1-3 rings, one or more of which include O, N, or S, preferably N. Examples of heteroaryls include indole, benzopyranone, benzoxazole, benzothiazole,

In embodiments of the compound of the present invention, Ar₁ is phenyl or phenyl substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and heterocyclyl.

In preferred embodiments of the compounds of the present invention, Ar₁ is phenyl or phenyl substituted with one or more substituents selected from the group consisting of

C₁-C₆ alkoxy, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, azido, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylthio, nitro, cyano, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, and heterocyclyl.

Embodiments of the compounds of the present invention include compounds
5 wherein Ar₁ is phenyl, phenyl substituted with one or more C₁-C₆ alkoxy, particularly phenyl substituted with one or more methoxy or propoxy. Embodiments of the compounds of the present invention also include compounds wherein Ar₁ is phenyl substituted with one or more halo, particularly, one, two, or three chloro or fluoro. Embodiments of the compounds of the present invention also include compounds wherein Ar₁ is phenyl
10 substituted with one or more C₁-C₆ dialkylamino, particularly N,N-dimethylamino. Embodiments of the compounds of the present invention further include compounds wherein Ar₁ is phenyl substituted with one or more azido, nitro, and cyano. Embodiments of the compounds of the present invention also include compounds wherein Ar₁ is phenyl substituted with one or more C₁-C₆ dialkyl sulfonamido, particularly N,N-dimethyl
15 sulfonamido. Embodiments of the compounds of the present invention also include compounds wherein Ar₁ is phenyl substituted with one or more C₁-C₆ alkylcarbonyloxy, particularly acetoxyl. Embodiments of the compounds of the present invention also include compounds wherein Ar₁ is phenyl substituted with one or more C₁-C₆ alkylcarbonylamino, particularly acetylamino. Embodiments of the compounds of the present invention also
20 include compounds wherein Ar₁ is phenyl substituted with one or more C₁-C₆ alkylthio, particularly methylthio. Embodiments of the compounds of the present invention also include compounds wherein Ar₁ is phenyl substituted with one or more heterocyclyl, particularly diazoly.

In accordance with the present invention, embodiments include compounds wherein
25 Ar₂ is phenyl, optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, and C₁-C₆ alkyloxycarbonyl. In a preferred embodiment, Ar₂ is phenyl.

In accordance with the present invention, embodiments also include compounds wherein Ar₂ is indolyl or indolyl substituted with one or more substituents selected from the
30 group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, and C₁-C₆ alkyloxycarbonyl. In a preferred embodiment, Ar₂ is indolyl, particularly indolyl substituted with one or more C₁-C₆ alkylcarbonyloxy. In another preferred embodiment, Ar₂ is benzopyranonyl.

In accordance with the present invention, embodiments include compounds wherein Ar_3 is phenyl, indolyl, or pyridyl, optionally substituted with one or more substituents selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, amino, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 trialkylamino, and nitro. In a particular embodiment, Ar_3 is phenyl, optionally substituted with one or more C_1 - C_6 trialkylamino, preferably N,N,N -trimethylamino. In another embodiment, Ar_3 is indolyl.

In accordance with an embodiment of the present invention, Q is Ar_3Q_1 and Q_1 is C_1 - C_6 alkylene carbonyloxy C_1 - C_6 alkyl, optionally having a C_1 - C_6 trialkylamino, for example, Q_1 is trimethylamino ethylene carbonyloxy t -butyl.

In accordance with another embodiment, Q is Q_1Ar_3 , wherein Q_1 is C_1 - C_6 alkylene, optionally having a C_1 - C_6 trialkylamino or a heterocyclic containing a quaternized nitrogen atom. Examples of Q_1 include methylene and trimethylamino ethylene, and ethylene having a N -alkyl pyrrolidiny, N -alkyl piperidiny, or N,N -dialkyl- N -tetrahydropyrany substituent. In certain embodiments, Q_1 is a covalent bond, preferably a single bond, e.g., when Ar_3 is N -methyl pyridiny and Z is $NH(C=O)$ or $NR(C=O)$.

In a preferred embodiment of the compound of the present invention, Z is $NH(C=O)$ or $NR(C=O)$, more preferably $NH(C=O)$.

In an embodiment of the present invention, Q_1 is a zwitterion, for example, an internal salt of a natural or synthetic amino acid. In another embodiment of the present invention, Q_1 is a group containing amidine or guanidine function wherein the amidine or guanidine may be optionally N -substituted with a C_1 - C_6 alkyl.

In a preferred embodiment of the compounds of the present invention, t is 0. In a particularly preferred embodiment, R_1 - R_4 are H . In another preferred embodiment, q and r are independently 1-7. In yet another preferred embodiment, p is 1-4. Still further preferred embodiments include compounds wherein q and r are 1, q and r are 2, and one of q and r is 1 and the other of q and r is 2.

In an embodiment of the compound of the present invention, X is selected from the group consisting of CH_2O , $(C=O)O$, and covalent bond. In another embodiment of the compound of the present invention, Y is selected from the group consisting of covalent bond and O . An example of a covalent bond is a single bond. In yet another embodiment of the present invention Z is selected from the group consisting of $O(C=O)$, covalent bond, $NH(C=O)$, $NR(C=O)$, O , NR , and $^+NR_2$.

Specific compounds of the present invention include compounds wherein Ar₁ is phenyl or a phenyl substituted with chloro, fluoro, methylthio, methoxy, isopropoxy, N,N-dimethylamino, azido, nitro, acetoxy, cyano, acetylamino, sulfonamido, or diazoly; X is CH₂O, (C=O)O, or single bond; Ar₂ is phenyl, indolyl, or benzopyranonyl, each of the Ar₂ may be substituted with methoxycarbonyl; Y is O, (C=O)O, or single bond; L is (CH₂)_n wherein n is 7-11; Z is O(C=O), NH(C=O), O, single bond, OCH₂, NCH₃, or N⁺; Q₁ is single bond, CH₂-CH(GU)-CH₂, (GU)CH-CH₂, CH₂CH(N⁺R₅R₆R₇)CH₂, wherein GU is guanidine, R₅, R₆, and R₇ are alkyl or heterocyclic or together with the N⁺ forms a heterocyclic; and Ar₃ is phenyl, N-methyl pyridinyl, N,N,N-trimethylaminophenyl, or nitrophenyl.

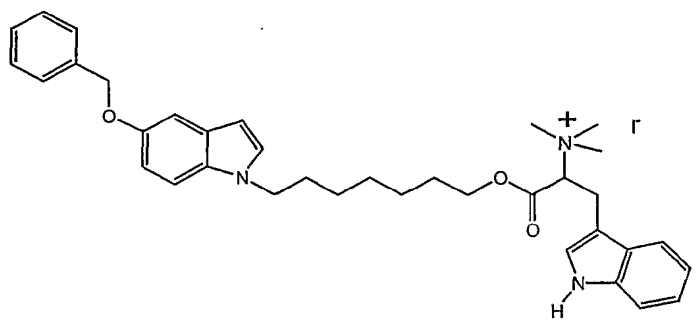
Specific embodiments include compounds wherein Ar₁ is phenyl, X is CH₂O, Ar₂ is phenyl or indolyl; Y is single bond or O; L is (CH₂)₇ or (CH₂)₈; Z is O, NH(C=O), O(C=O); Q₁ is single bond, n-propyl, CH₂, CH(NMe₃)CH₂, CH₂-CH(GU)-CH₂, (GU)CH-CH₂; and Ar₃ is phenyl, indolyl, hydroxyphenyl, nitrophenyl, and N,N,N-trimethylaminophenyl, wherein the hydroxy, nitro and N,N,N-trimethylamino groups may be present in the *o*-, *m*-, or *p*- position. Other embodiments include compounds wherein Ar₁ is *o*-, *m*-, or *p*-chlorophenyl; X is CH₂O; Ar₂ is phenyl; Y is O; L is (CH₂)₈; Z is NH(C=O) or O(C=O); Q₁ is CH₂, single bond, CH(NMe₃)CH₂, or CH(N-methylpyrrolidinyl)CH₂, and Ar₃ is phenyl, N-methyl pyridinyl, or N,N,N-trimethylaminophenyl. Further embodiments include compounds wherein Ar₁ is dichlorophenyl wherein the chlorine atoms may be in the 2,3; 2,4; 2,5; 2,6; 3,4; 3,5; or 3,6-position; X is (C=O)O or CH₂O; Ar₂ is phenyl; Y is O; L is (CH₂)₈; Z is NH(C=O); Q₁ is single bond, CH₂, CH(NMe₃)CH₂; and Ar₃ is phenyl, N-methyl pyridinyl, or N,N,N-trimethylaminophenyl. Additional embodiments include compounds wherein Ar₁ is trichlorophenyl wherein the chlorine atoms may be present in the 2,3,4; 2,4,5; 2,5,6; 3,4,5; or 3,5,6 position; X is (C=O)O; Ar₂ is phenyl; Y is O; L is (CH₂)₈; Z is NH(C=O); Q₁ is CH₂, CH(NMe₃)CH₂; and Ar₃ is phenyl or N,N,N-trimethylaminophenyl. Other embodiments include compounds wherein Ar₁ is *o*-, *m*-, or *p*-fluorophenyl; X is (C=O)O; Ar₂ is phenyl; Y is O; L is (CH₂)₈; Z is NH(C=O); Q₁ is CH(NMe₃)CH₂; and Ar₃ is phenyl. Further embodiments include compounds wherein Ar₁ is difluorophenyl wherein the fluorine atoms may be in the 2,3; 2,4; 2,5; 2,6; 3,4; 3,5; or 3,6-position; X is (C=O)O; Ar₂ is phenyl; Y is O; L is (CH₂)₈; Z is NH(C=O); Q₁ is CH(NMe₃)CH₂; and Ar₃ is phenyl. Additional embodiments include compounds wherein

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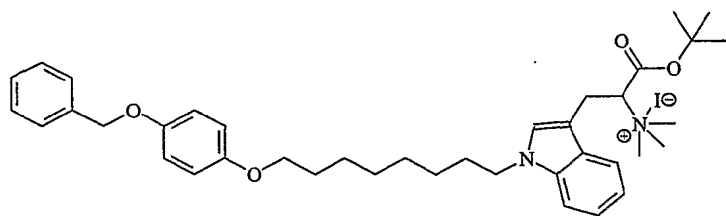
Ar₁ is trifluorophenyl wherein the fluorine atoms may be present in the 2,3,4; 2,4,5; 2,5,6; 3,4,5; or 3,5,6 position; X is (C=O)O; Ar₂ is phenyl; Y is O; L is (CH₂)₈; Z is NH(C=O); Q₁ is single bond, CH₂, or CH(NMe₃)CH₂; and Ar₃ is phenyl or N-methyl pyridinyl, or N,N,N-trimethylaminophenyl. Additional embodiments include compounds wherein Ar₁ is

5 methoxy phenyl or isopropoxy phenyl, wherein the methoxy or isopropoxy group may be present in the *o*-, *m*-, or *p*- position; X is (C=O)O or CH₂O; Ar₂ is phenyl; Y is O; L is (CH₂)₈; Z is NH(C=O) or O(C=O); Q₁ is single bond, CH₂, or CH(NMe₃)CH₂; and Ar₃ is phenyl or N-methyl pyridinyl, or N,N,N-trimethylaminophenyl. In the embodiments above Q is preferably Q₁Ar₃.

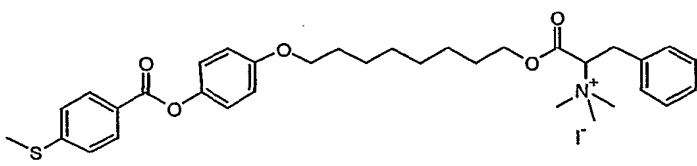
10 Particular examples of compounds of the present invention include:



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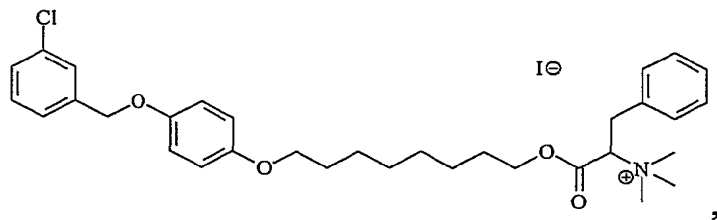


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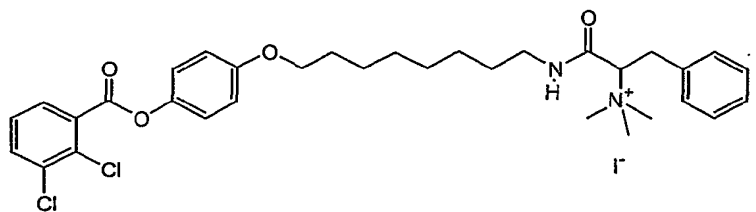
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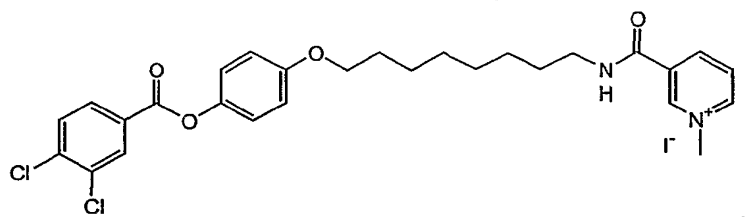
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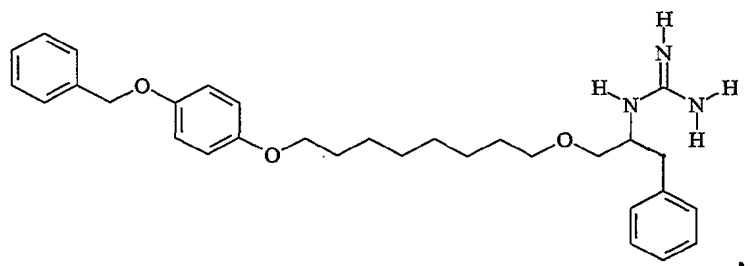
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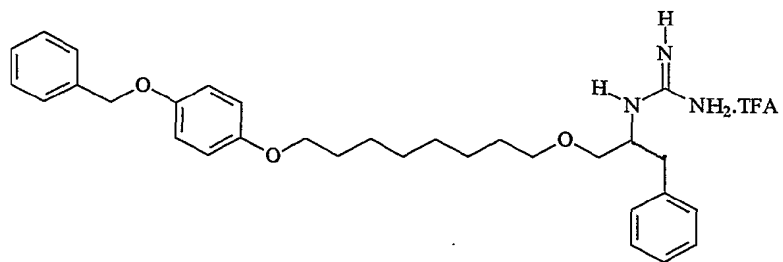
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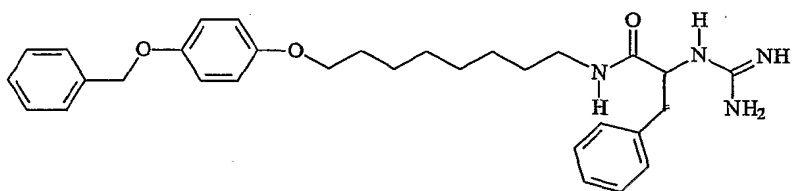


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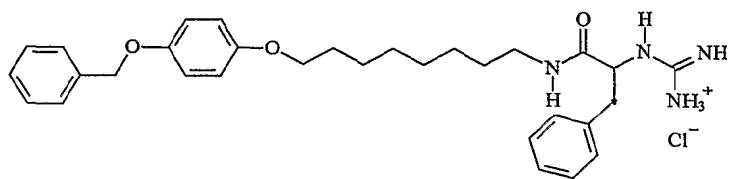


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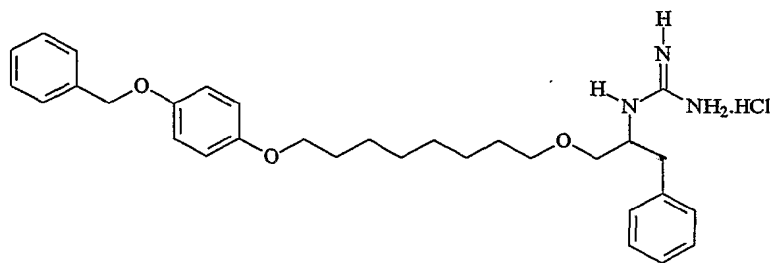


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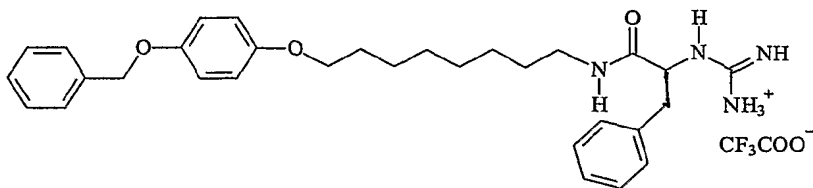


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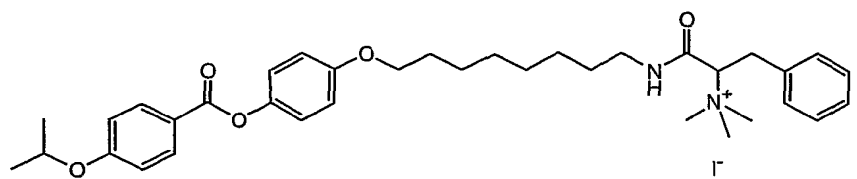
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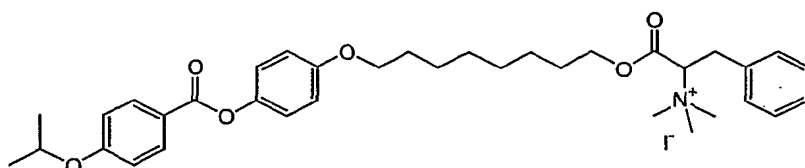
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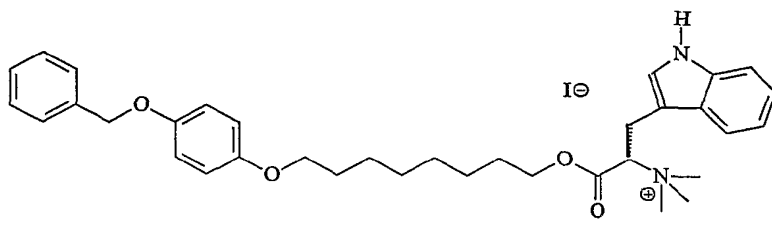


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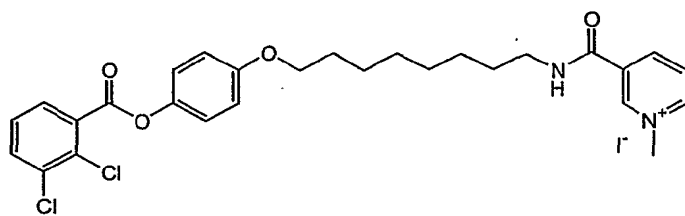


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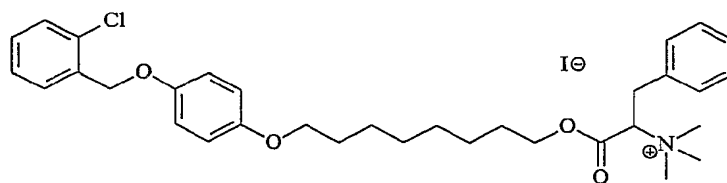
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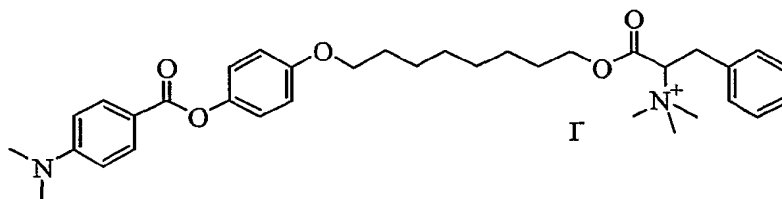
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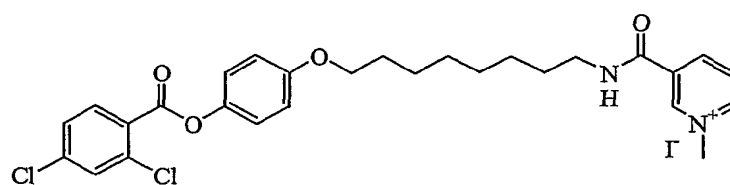
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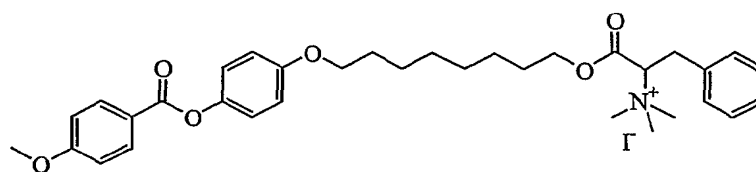
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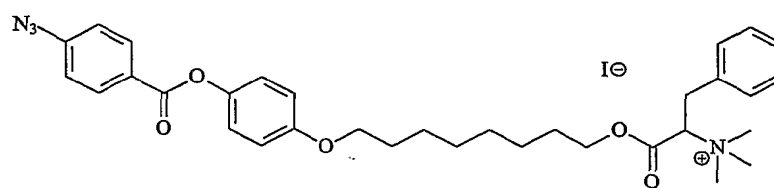
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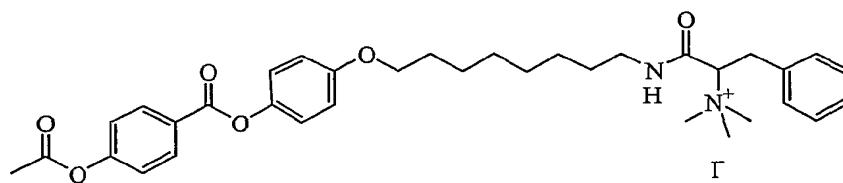
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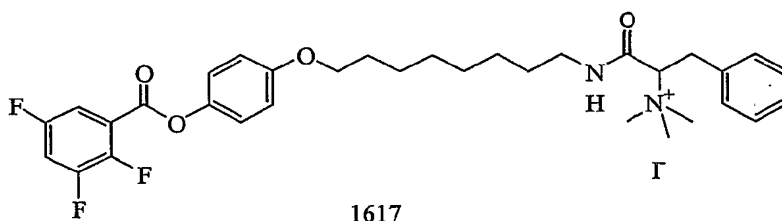
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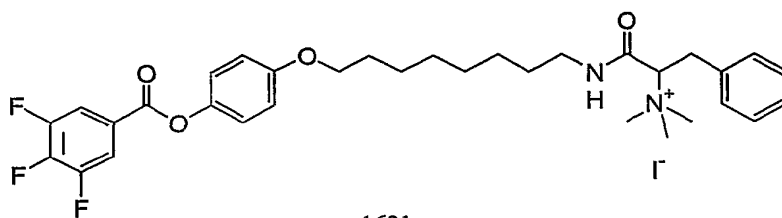
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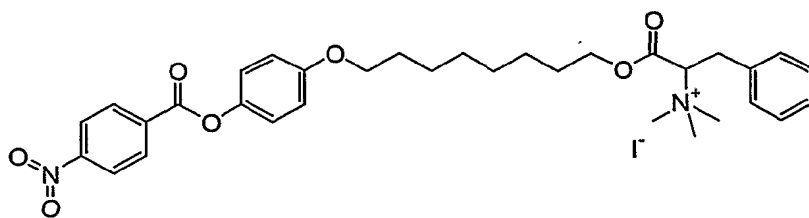
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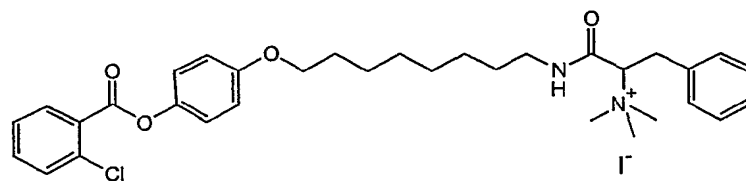


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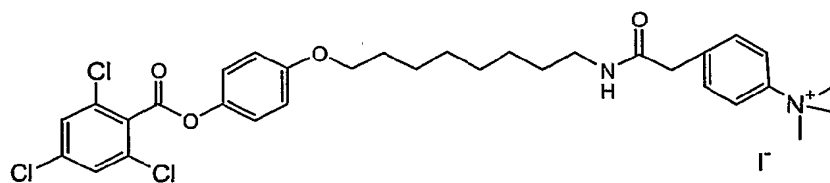


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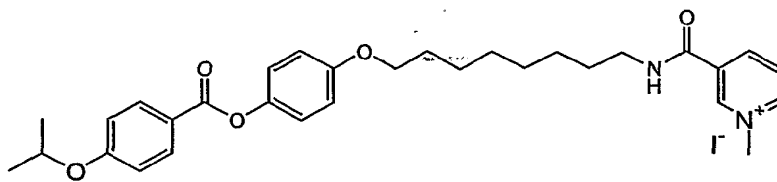
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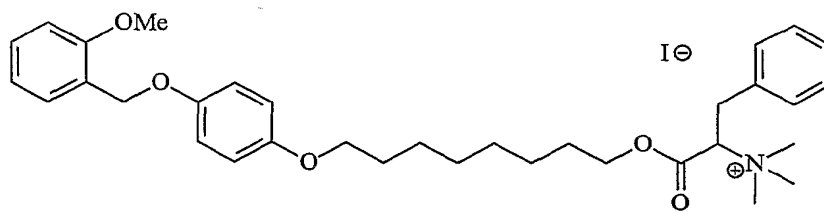
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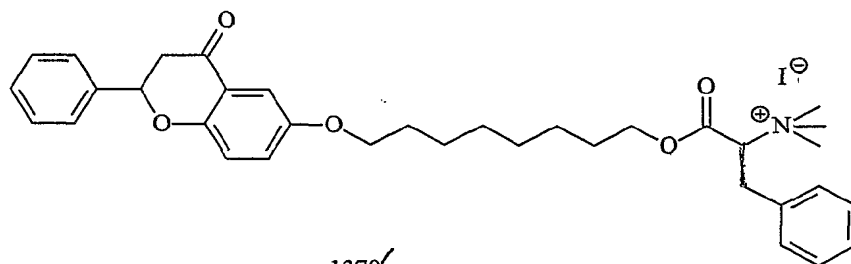
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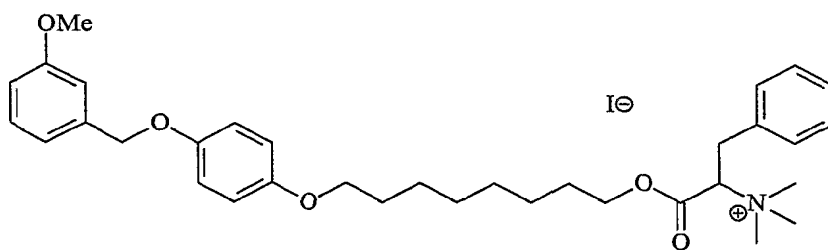
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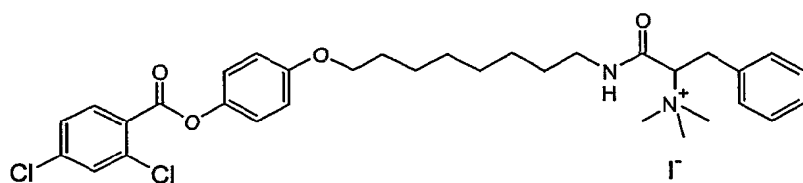


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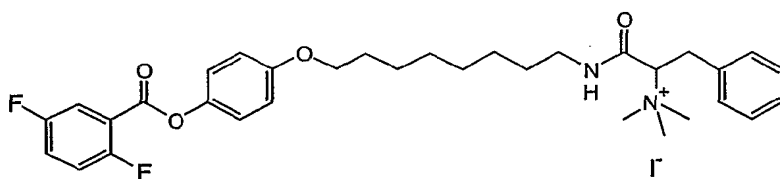
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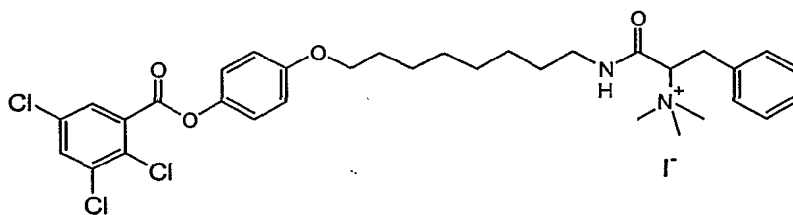
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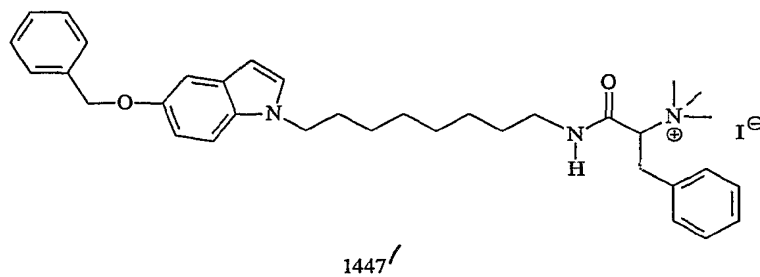
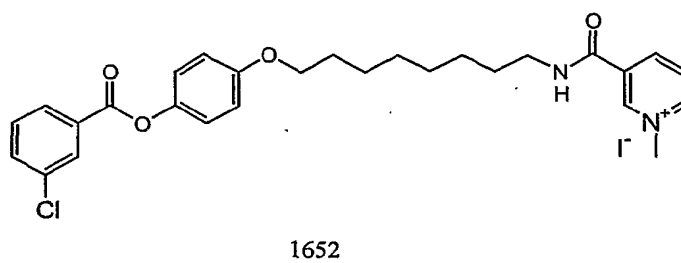
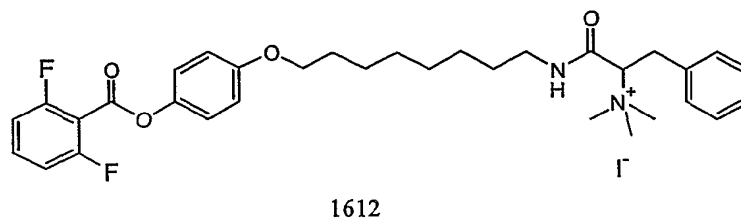
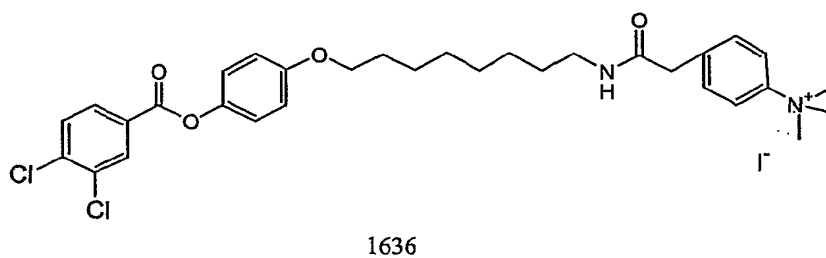
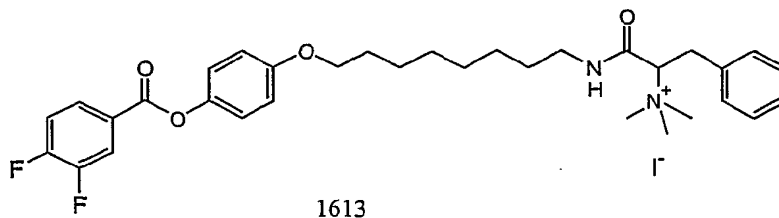


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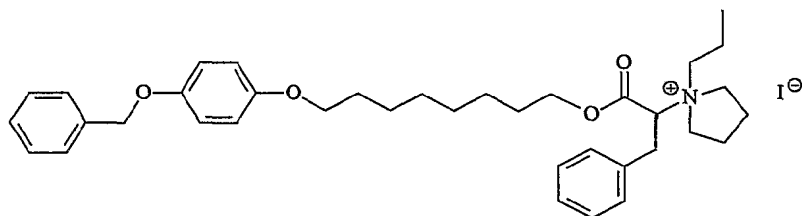


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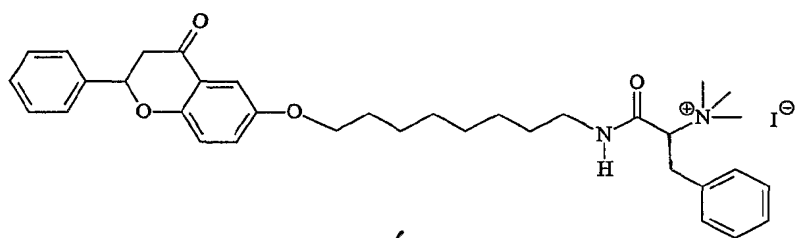


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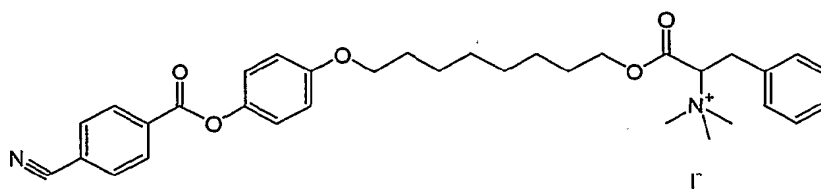
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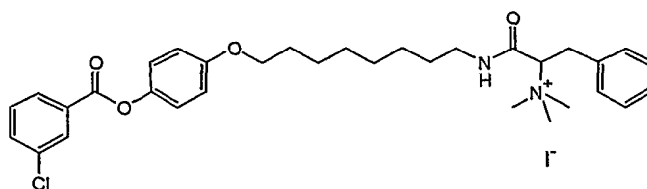


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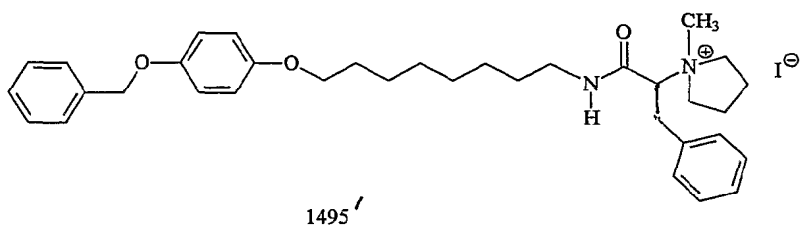
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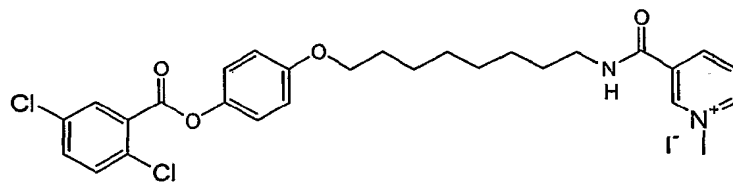
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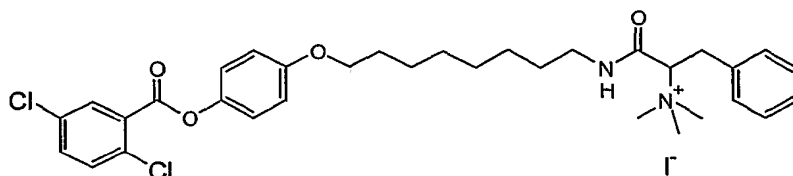


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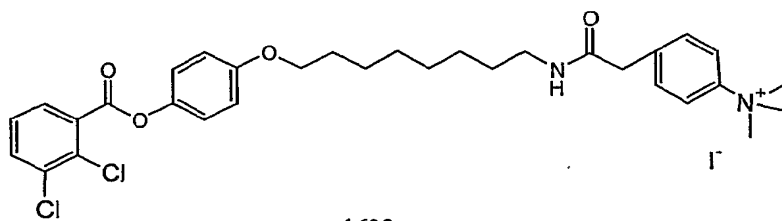


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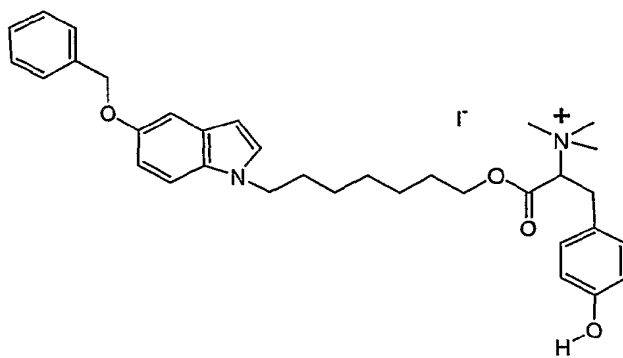


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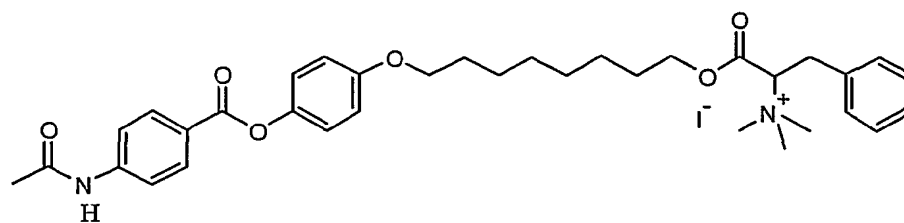
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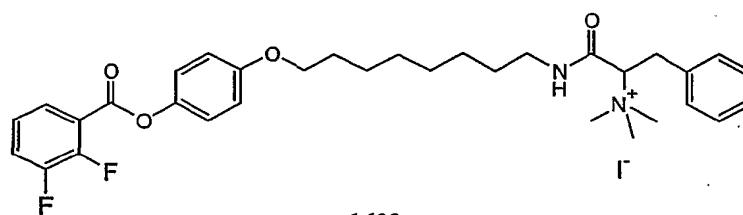
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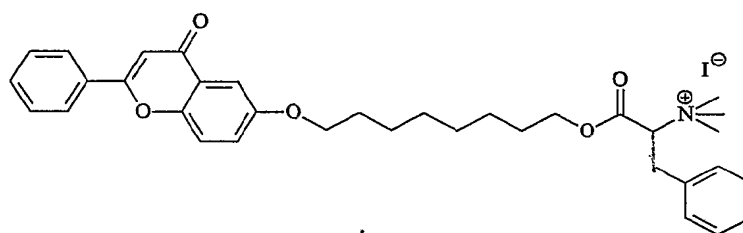
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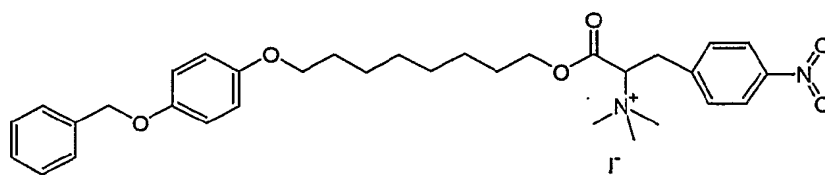
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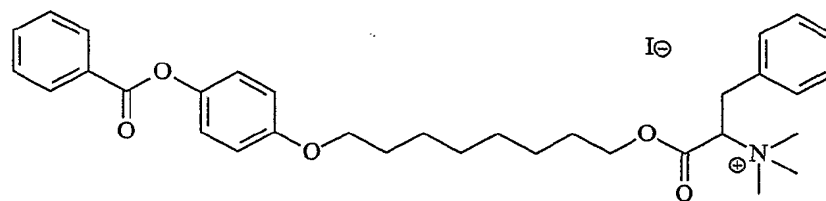
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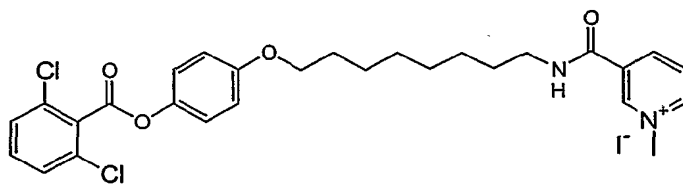


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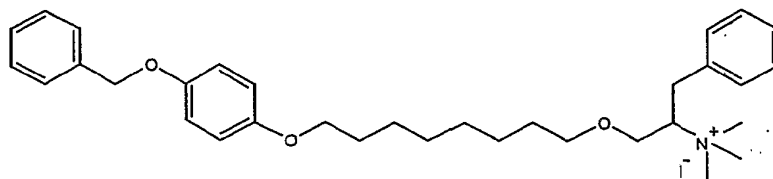
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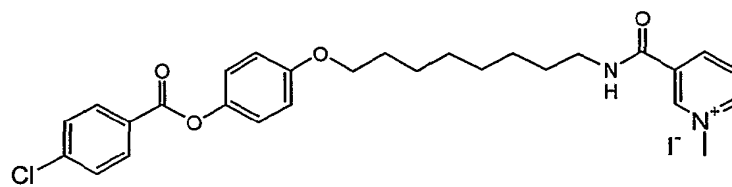


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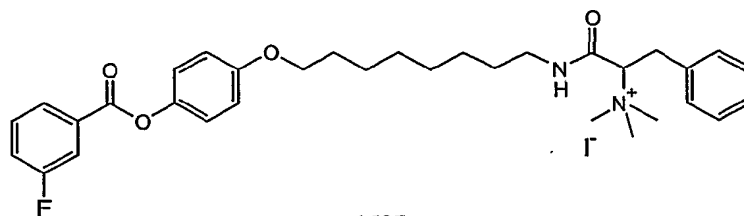
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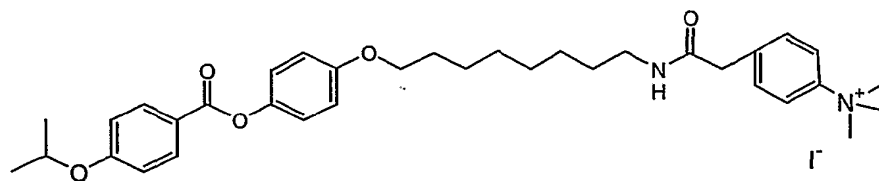


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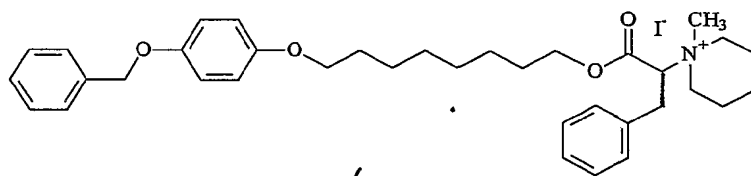
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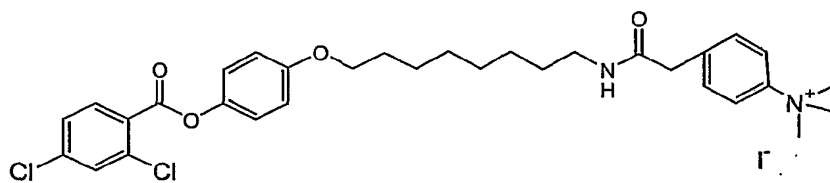
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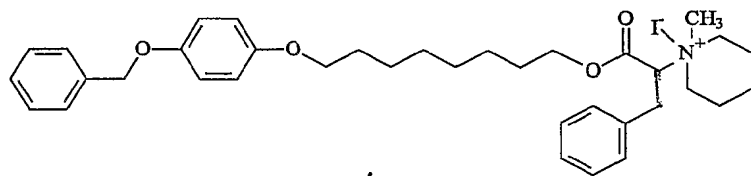
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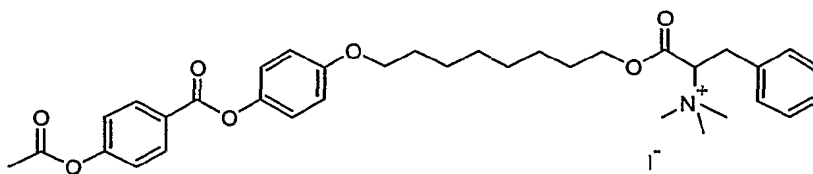
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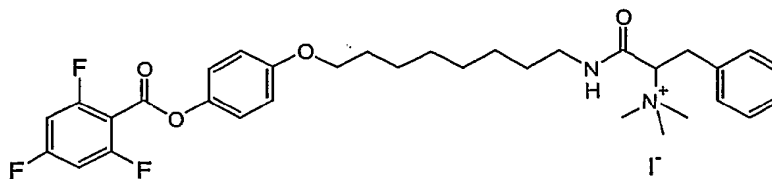
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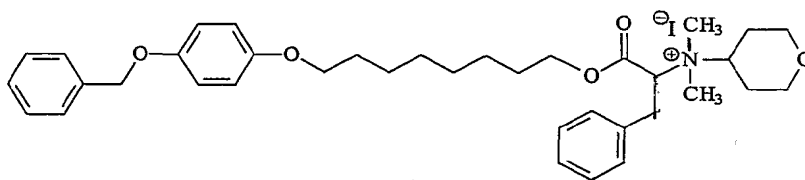


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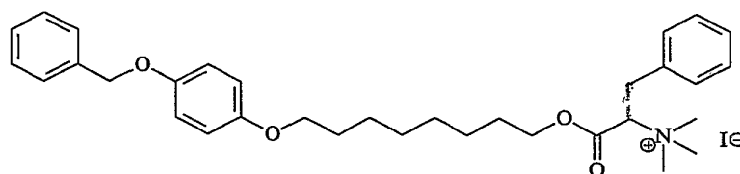


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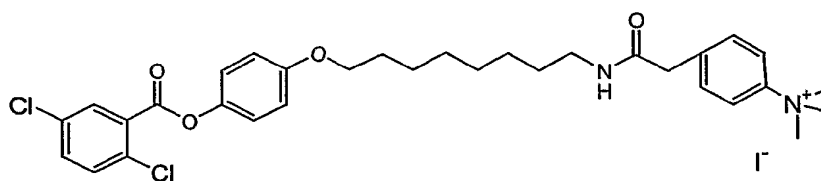


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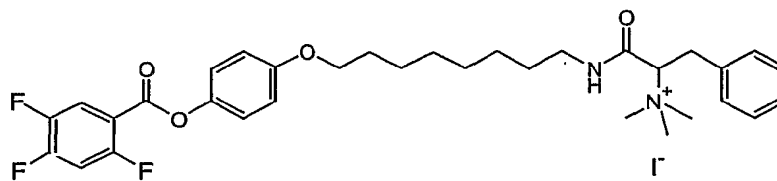
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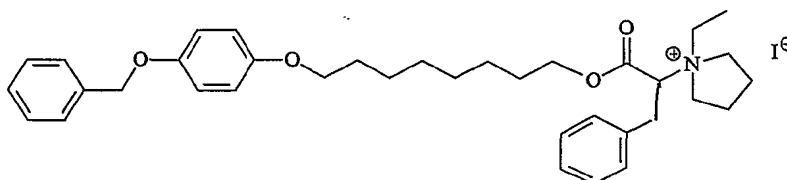
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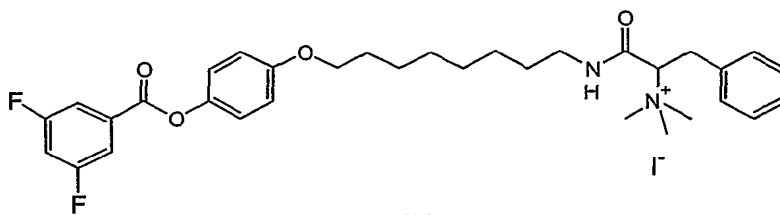
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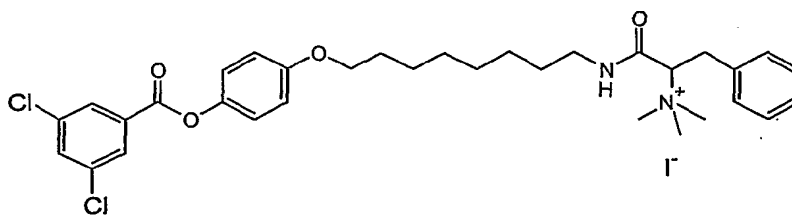


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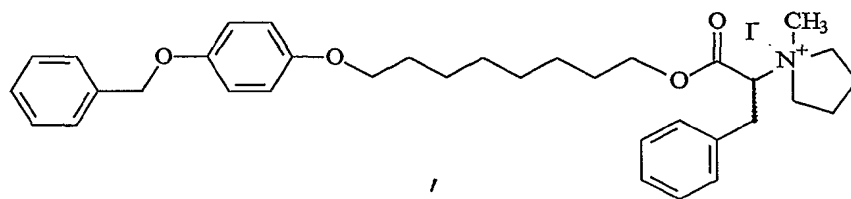
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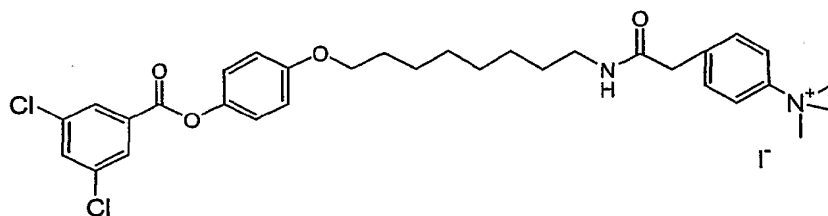
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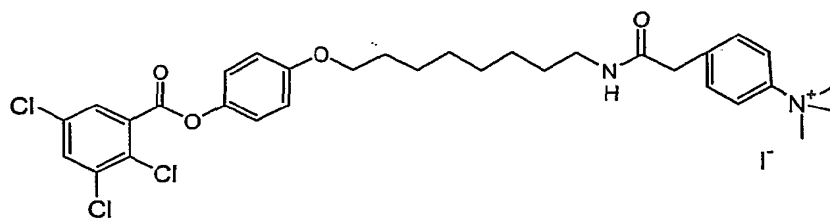
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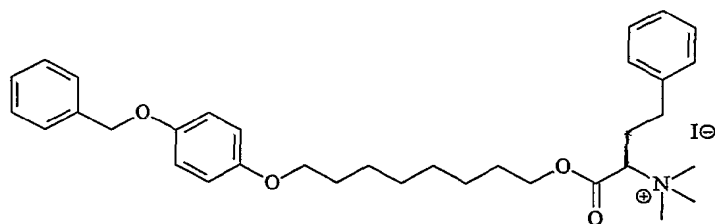


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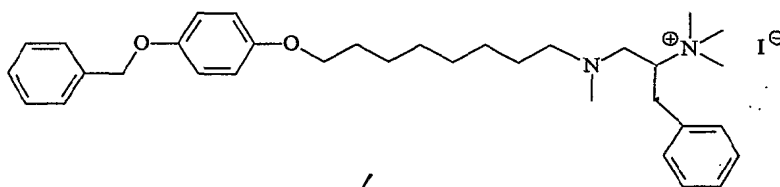


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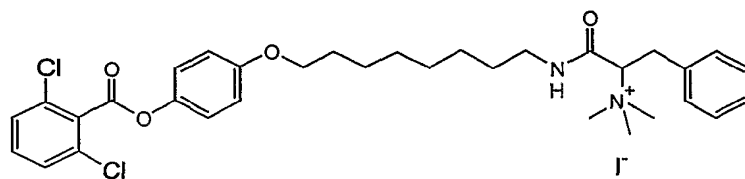


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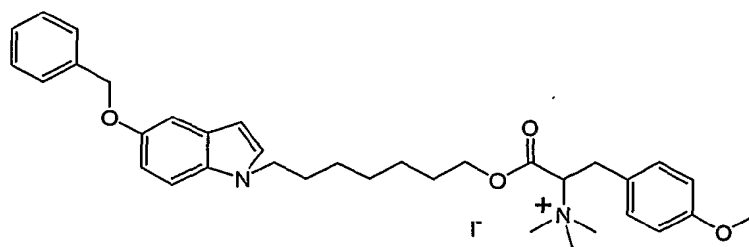
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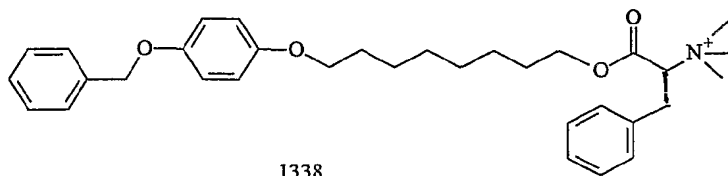


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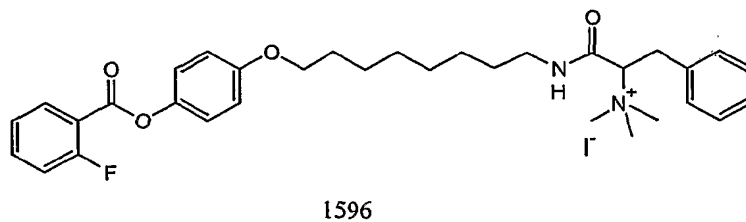
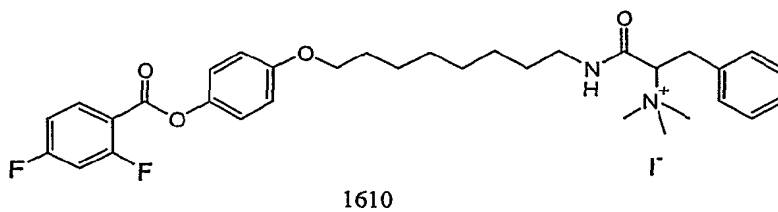
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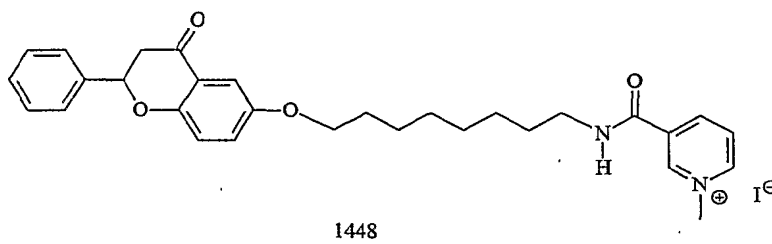
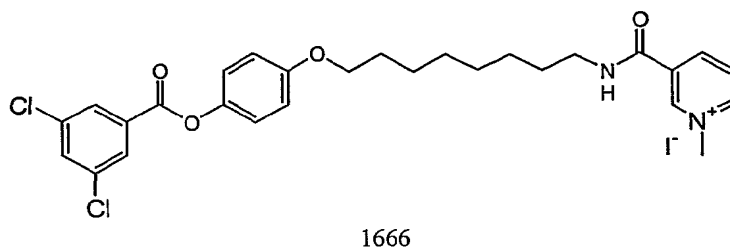
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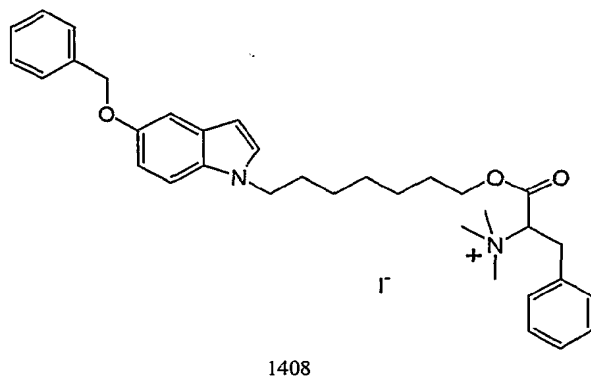
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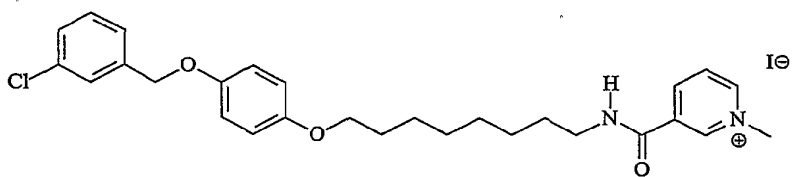
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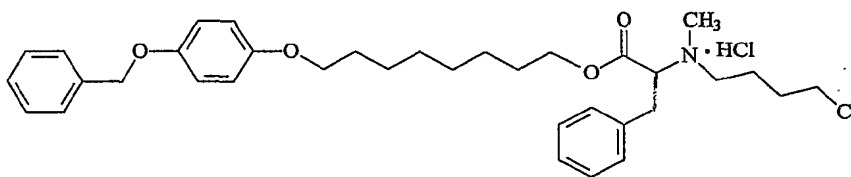


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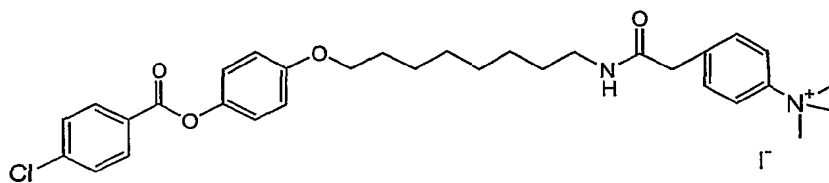


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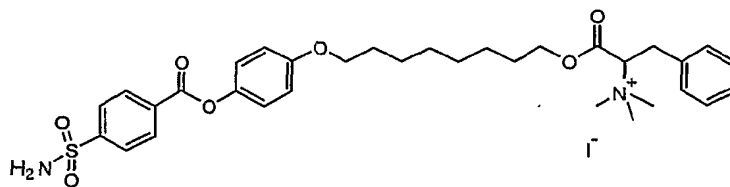


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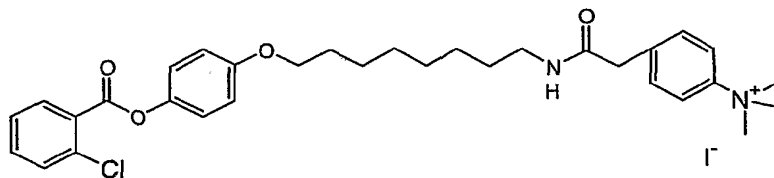


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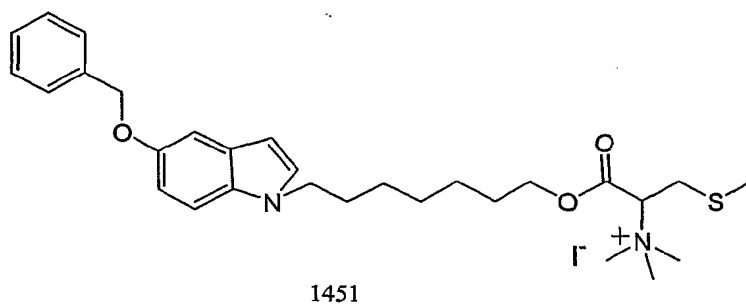
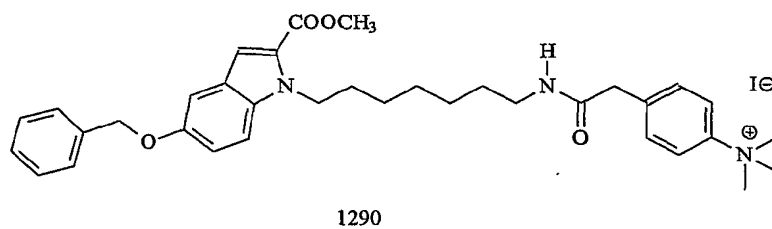
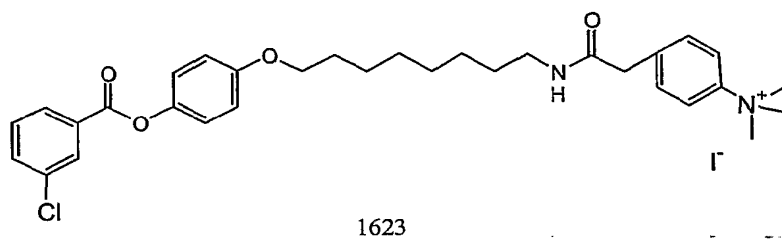
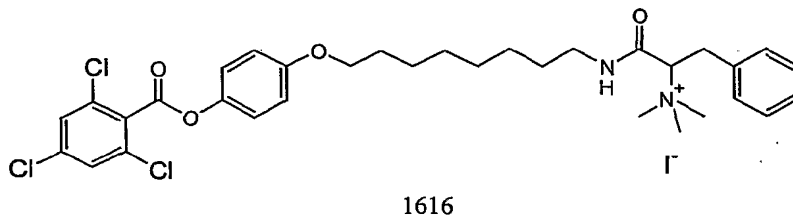
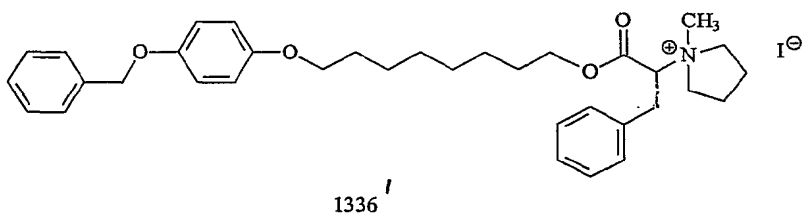
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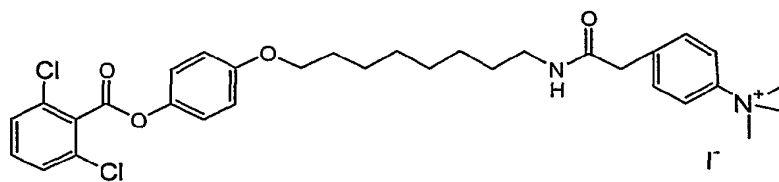
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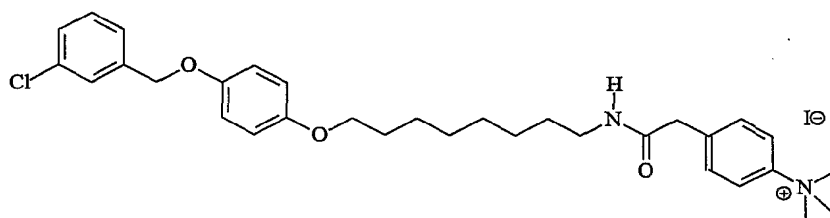


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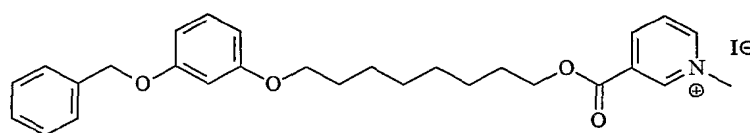


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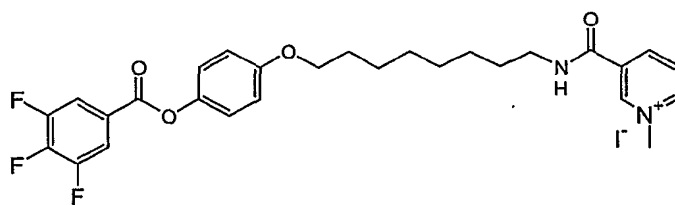


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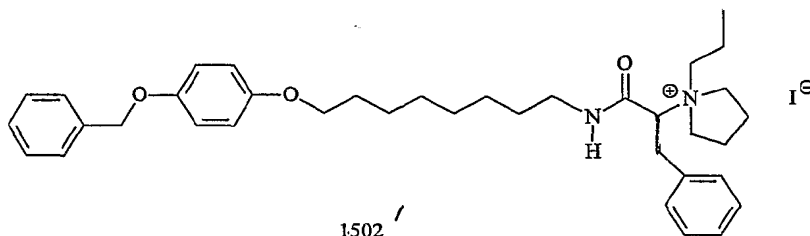
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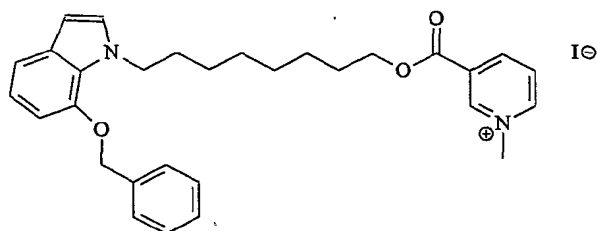
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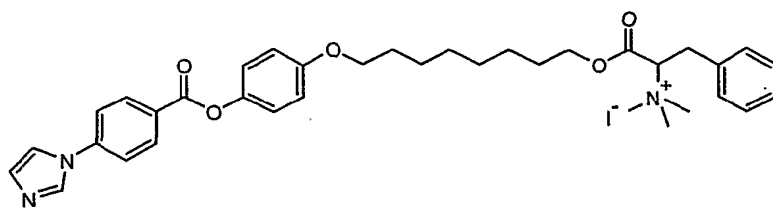


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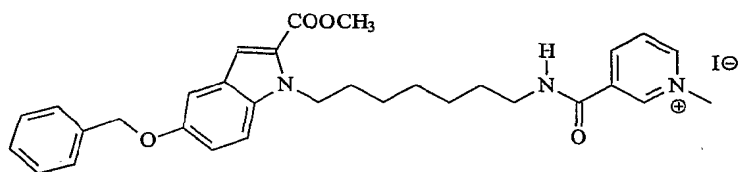


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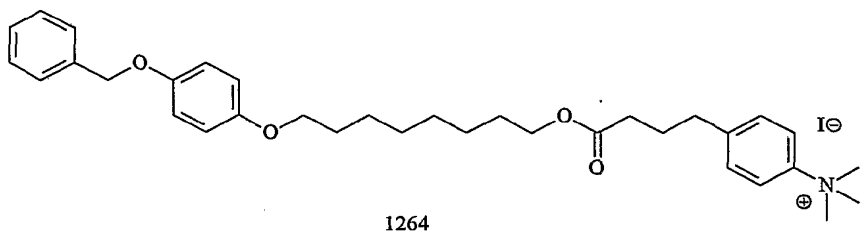


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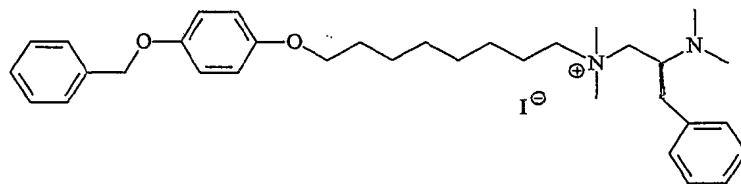


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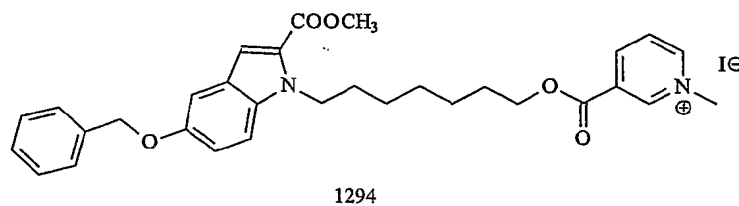
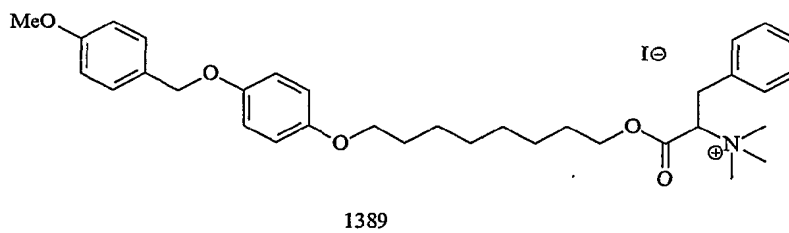
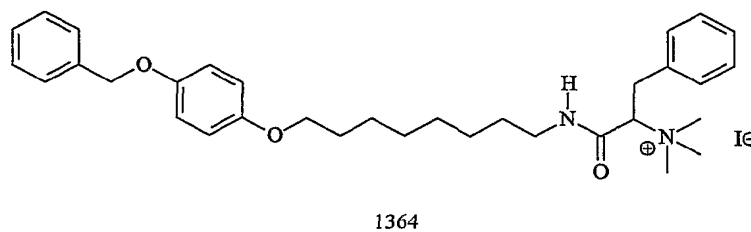
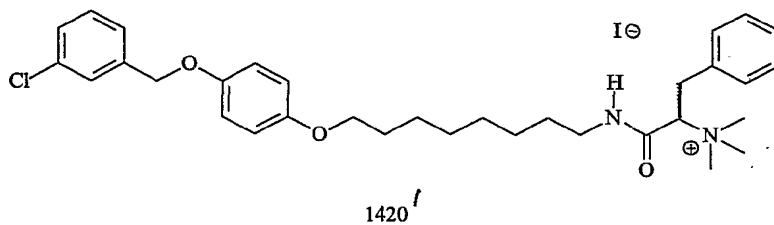
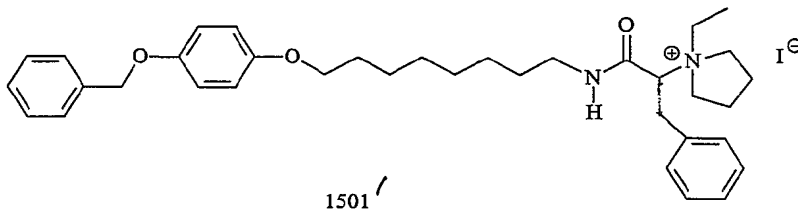
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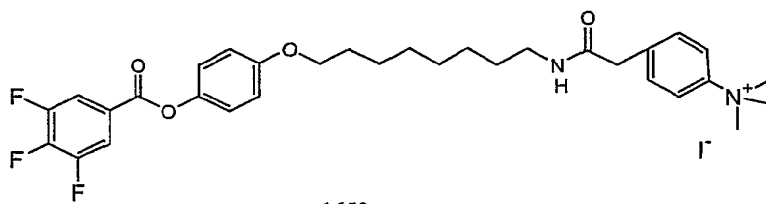
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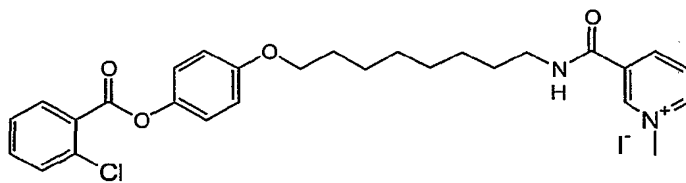
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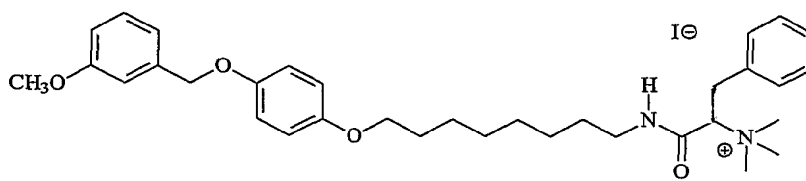
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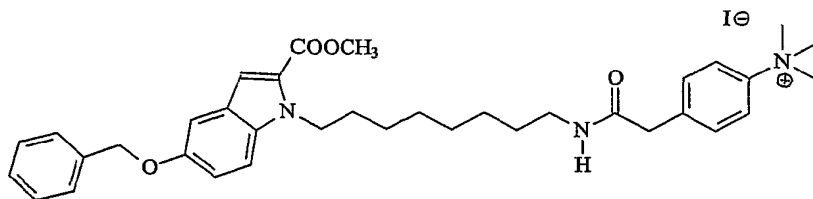
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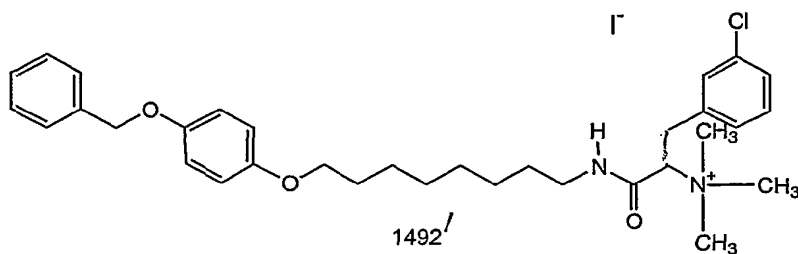
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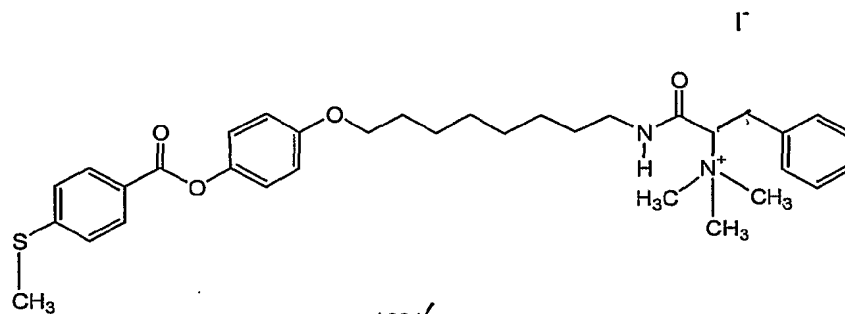


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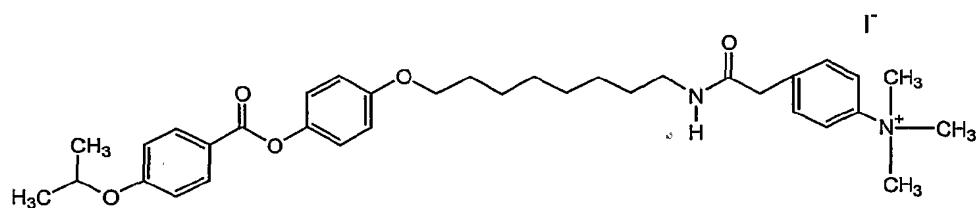
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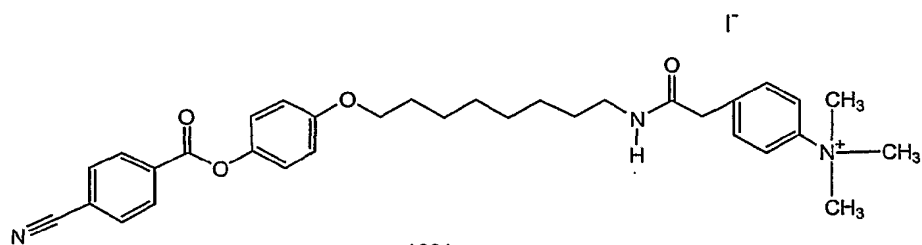
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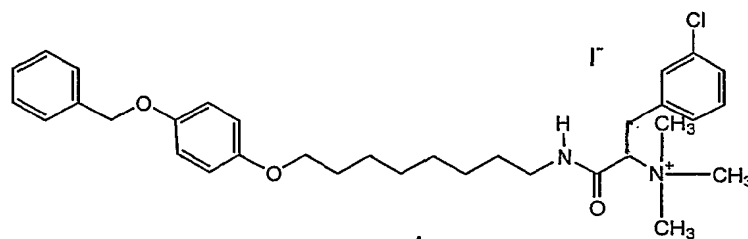
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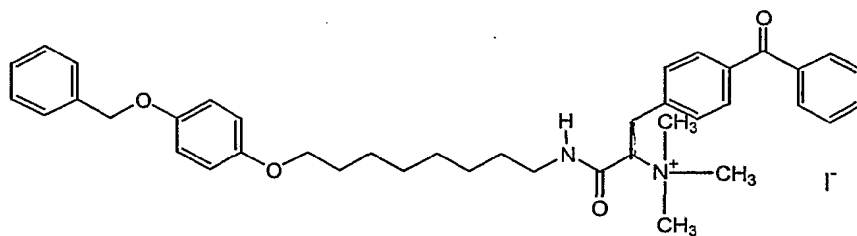
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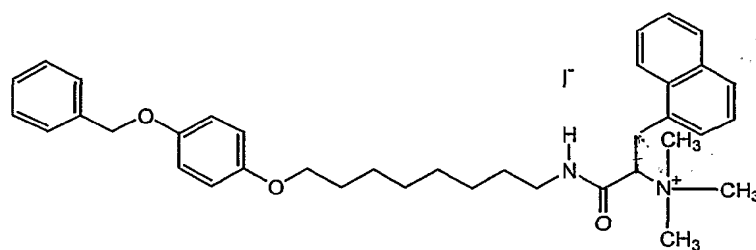
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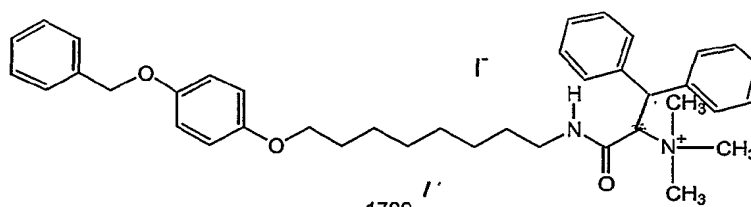
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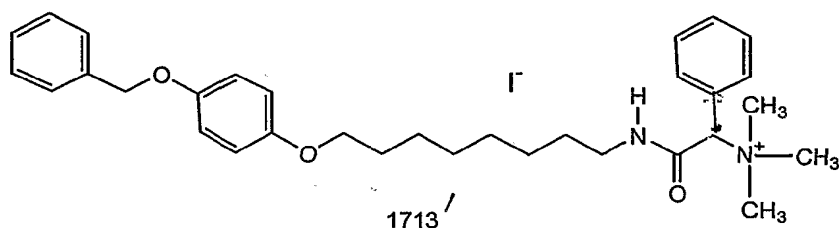
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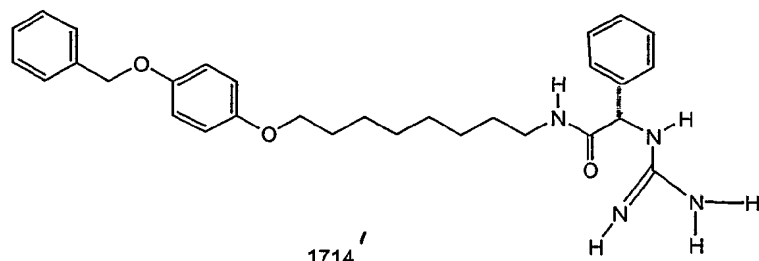
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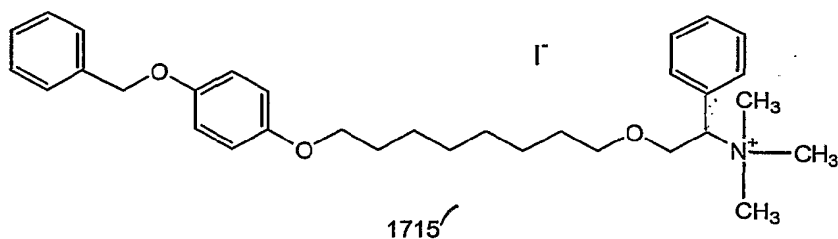
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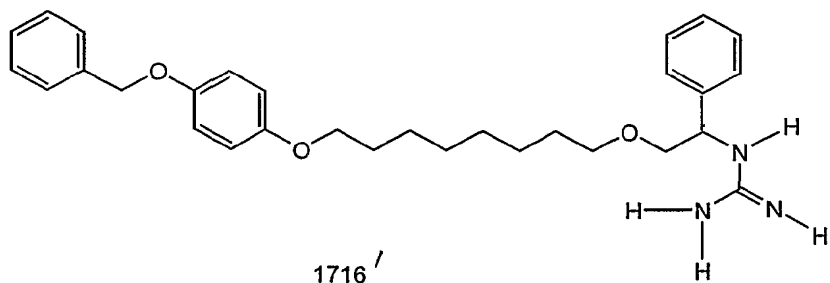
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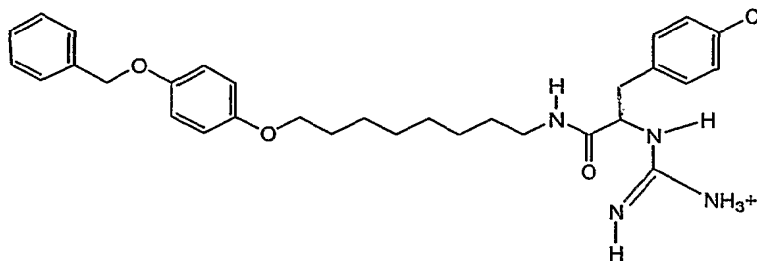
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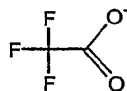


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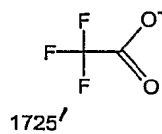
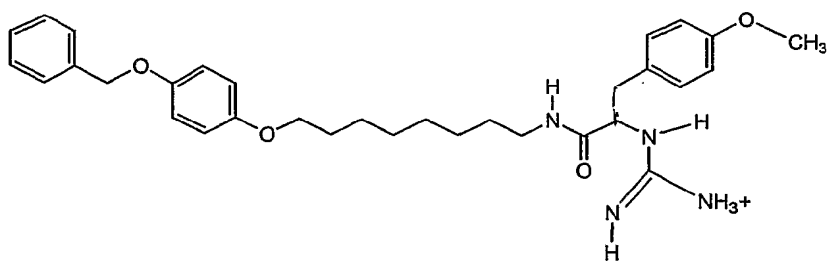
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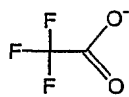
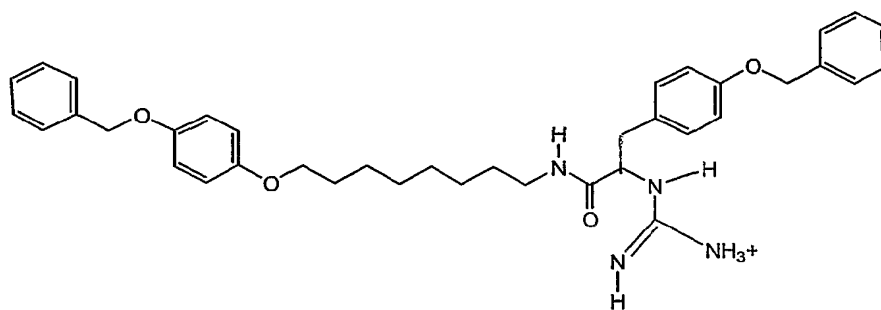


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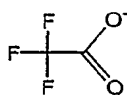
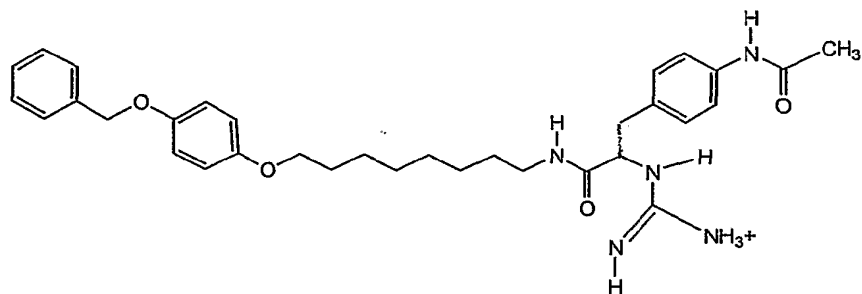


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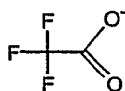
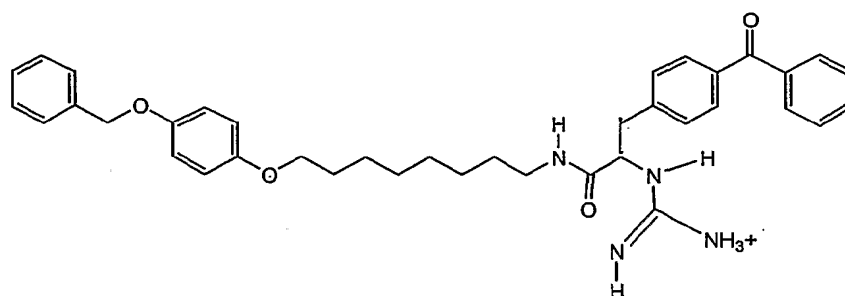
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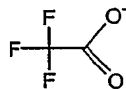
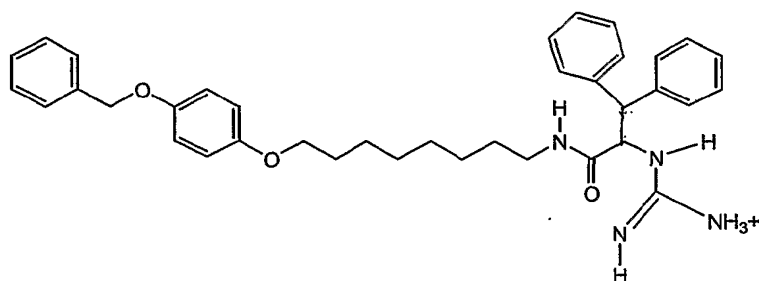
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1729 /

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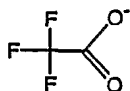
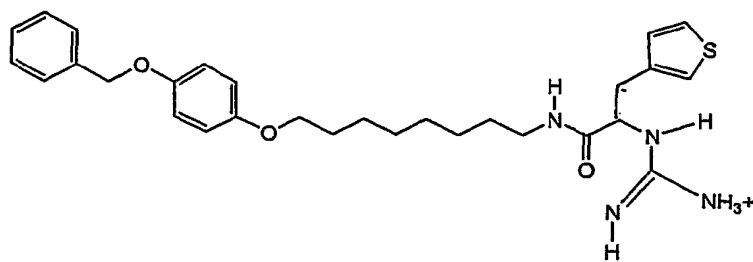
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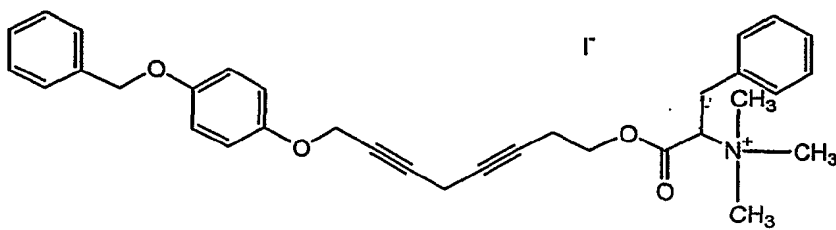
1738 /

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44

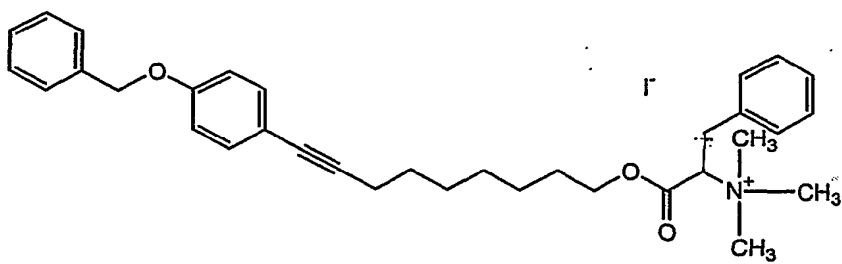


1741'



1752'

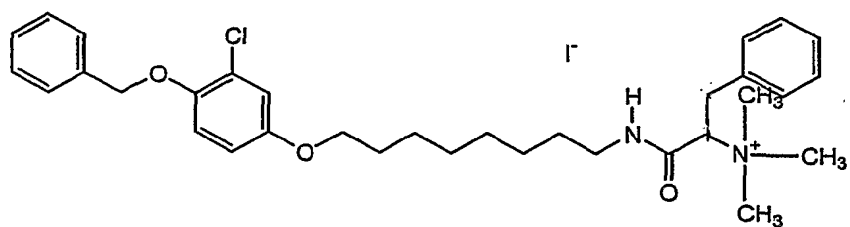
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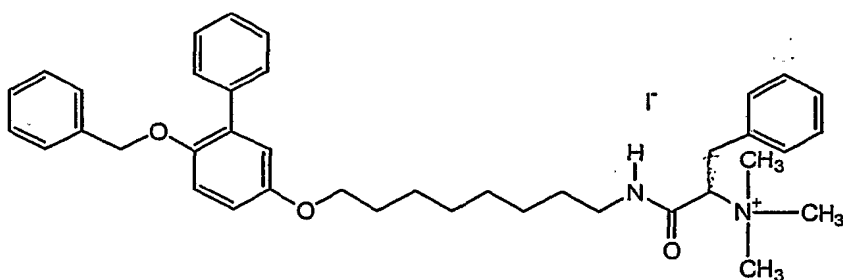
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1758

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1760'

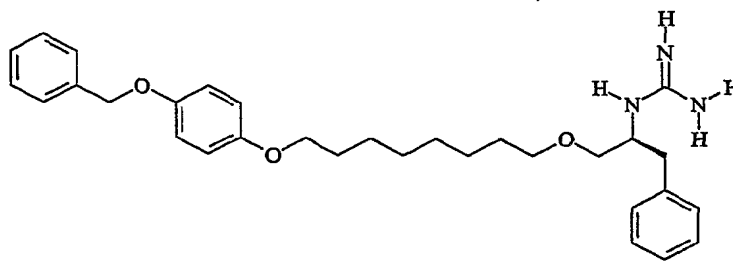
5

wherein Γ is a pharmaceutically acceptable anion.

The compounds described above can have a suitable configuration if an asymmetric center is present. Thus, the compounds may be in R, S, or a mixture of R and S forms.

10 Further, in the compounds described above, the amino acids employed may be the natural (L) form or the unnatural (D) form.

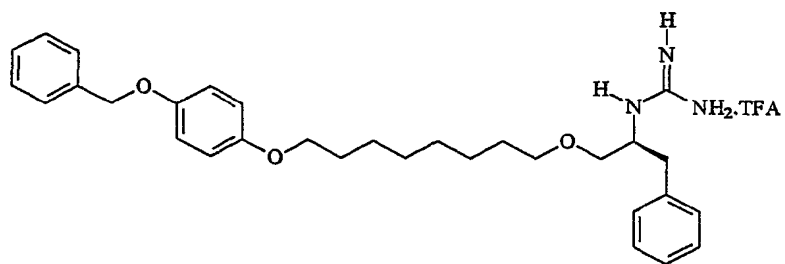
Embodiments of the above compounds of formula (I) include:



1679

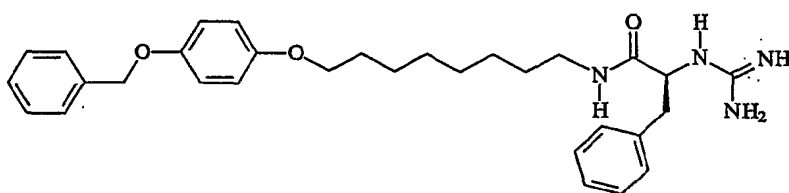
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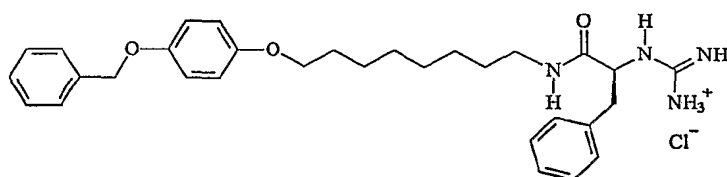
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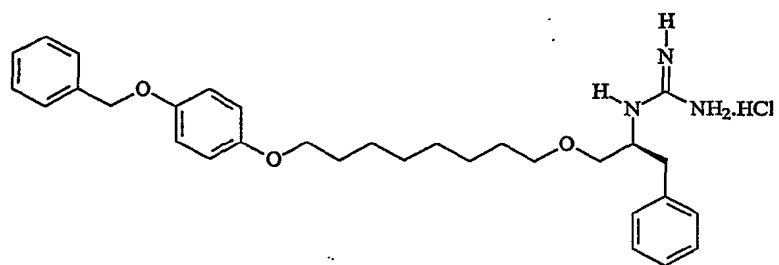
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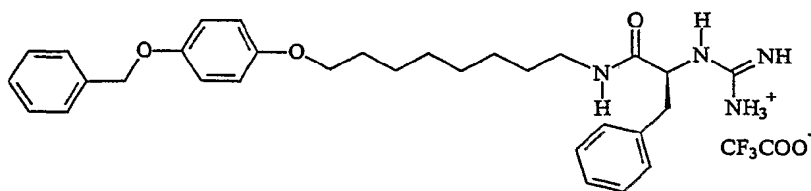


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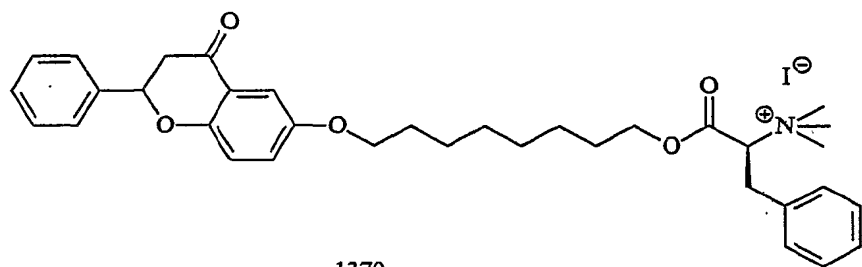


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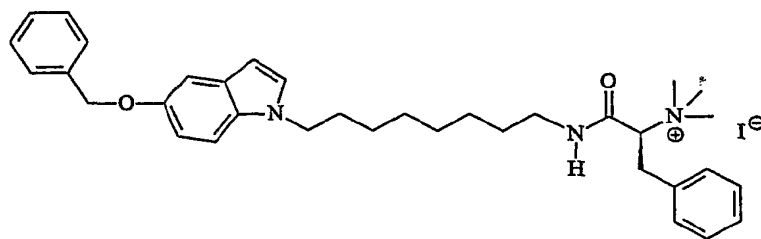
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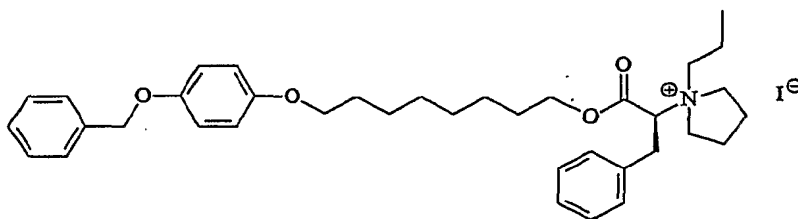
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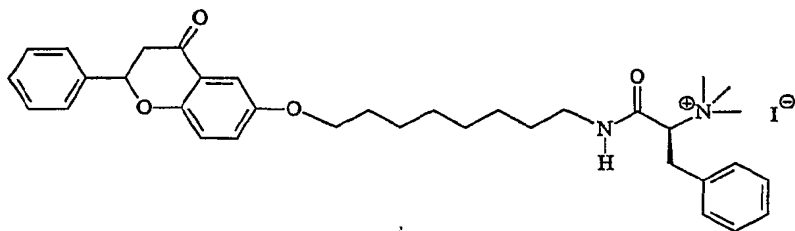
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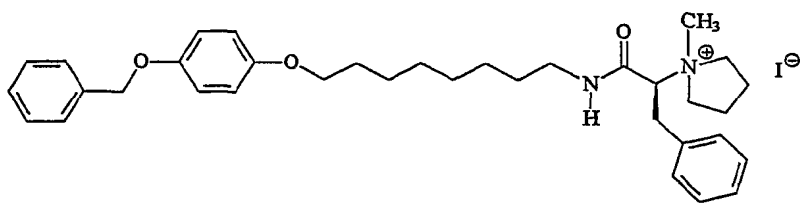
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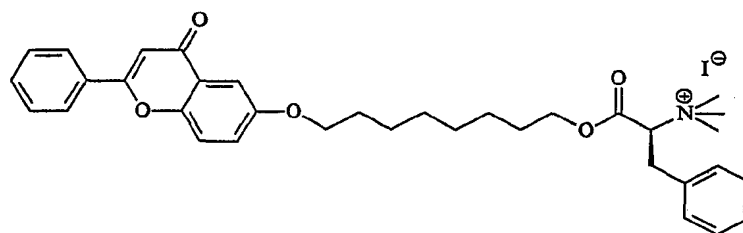
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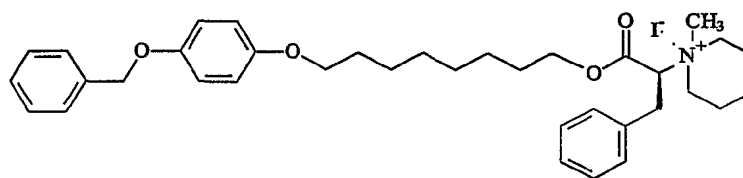


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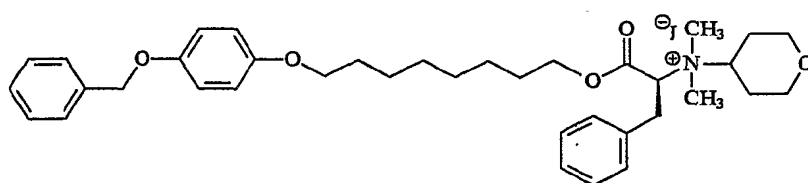
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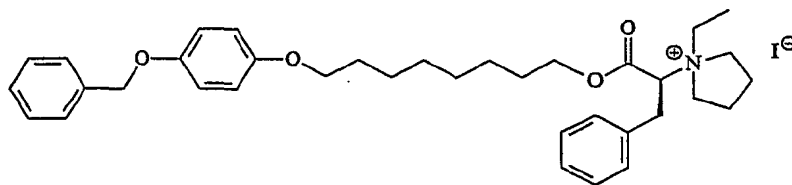


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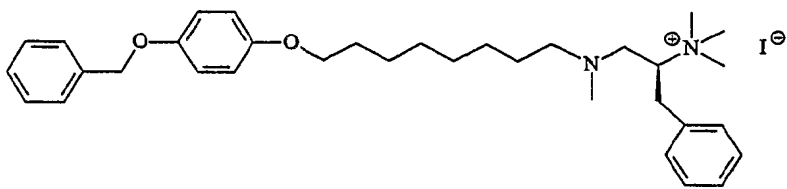
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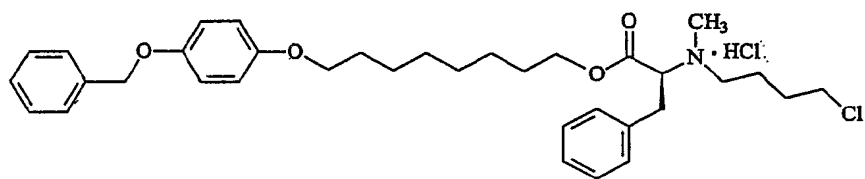


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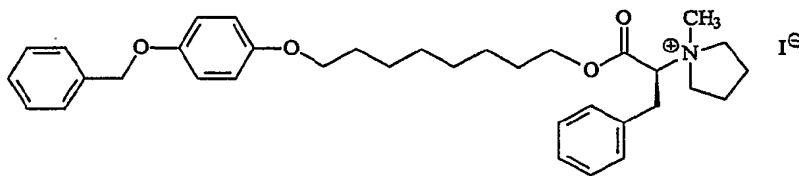


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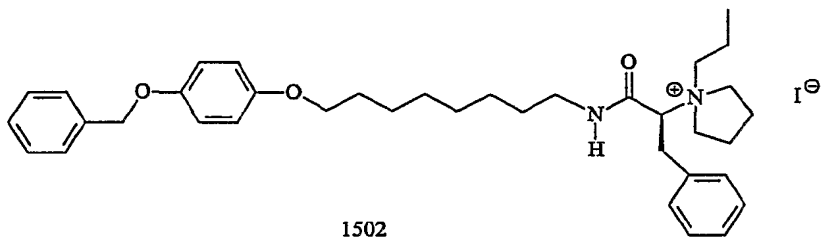


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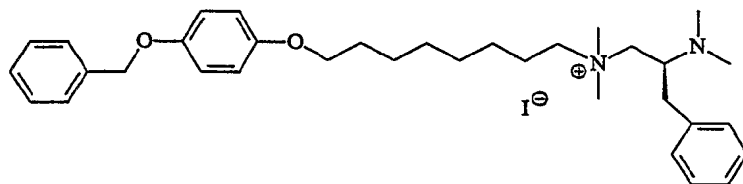
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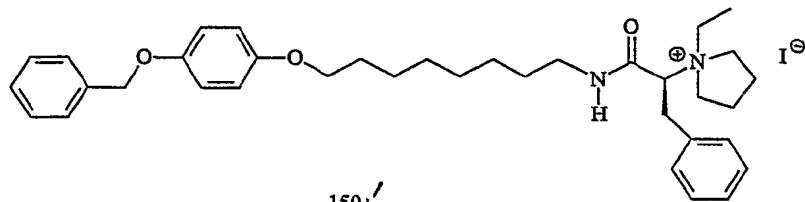


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, and

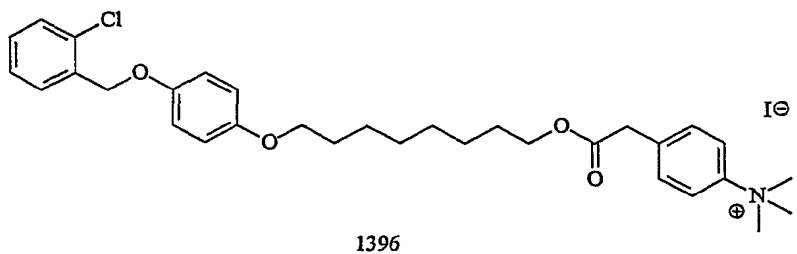
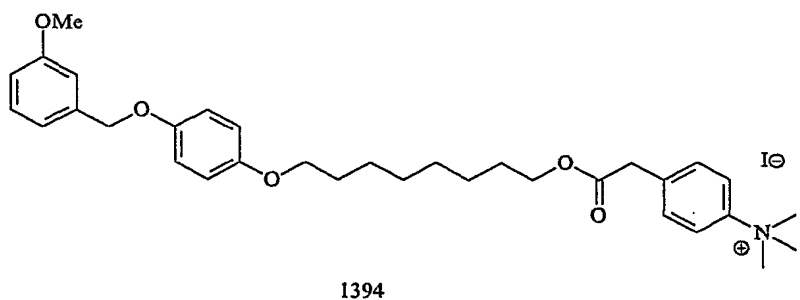
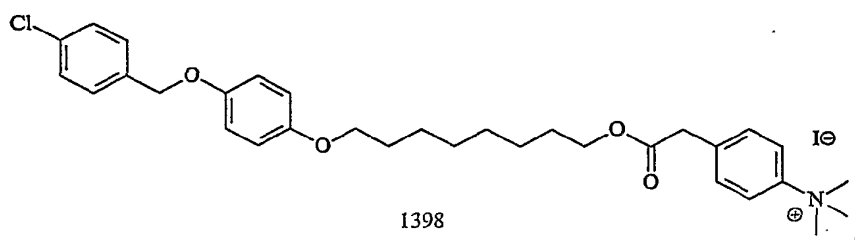


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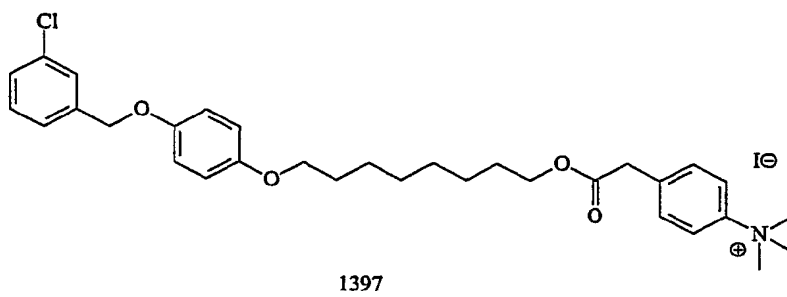
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The present invention provides in another embodiment, a compound of the formula $A-B-(CH_2)_n-O-CO-CH_2-Ph(NMe_3)^+ I^-$, wherein A is a phenyl or indole, optionally substituted with a benzyloxy group; B is a covalent bond or oxygen atom, and I^- is a pharmaceutically acceptable anion. For example, A is a phenyl group substituted with benzyloxy, chlorobenzyloxy, or methoxybenzyloxy group. The chloro or methoxy group can be in any of ortho, para, or meta positions. In embodiments, the chloro or methoxy group is in the ortho or para position. A further example includes a compound where A is an indole substituted with benzyloxy.

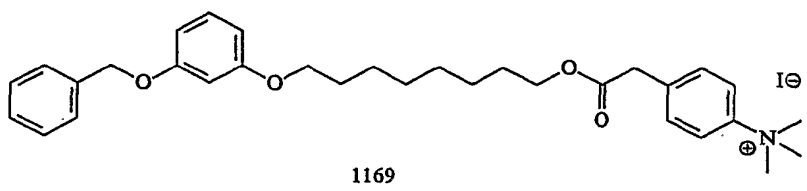
Specific examples of the compounds of the above embodiment of the present invention include compounds selected from the group consisting of:



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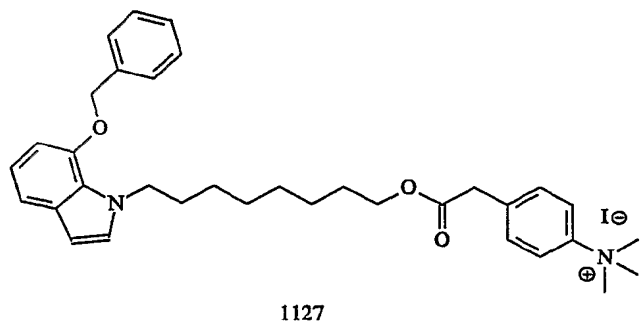


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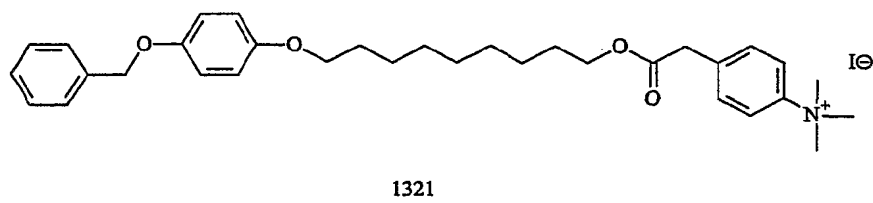


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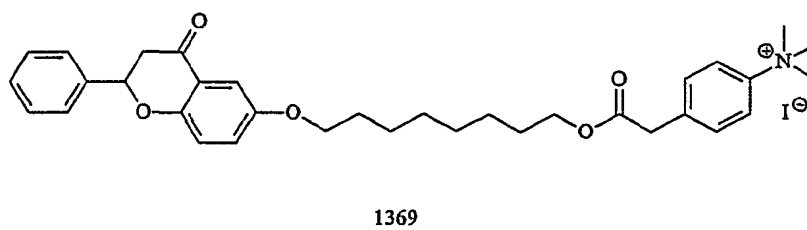
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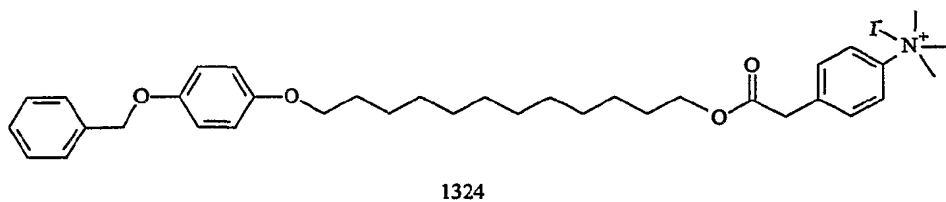
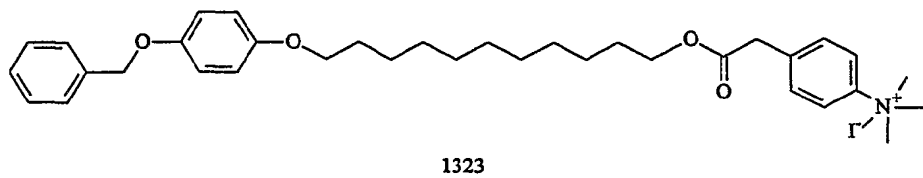
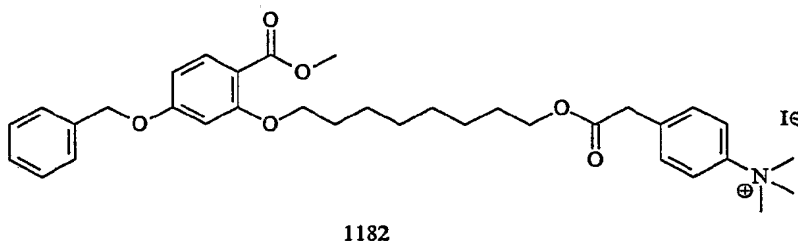
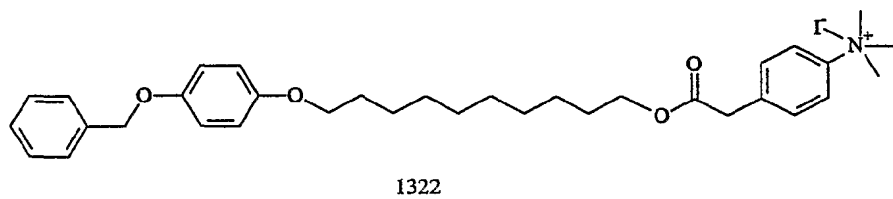
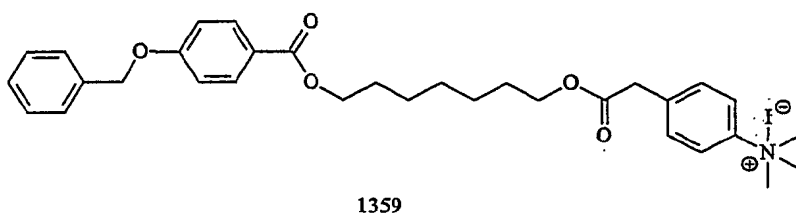
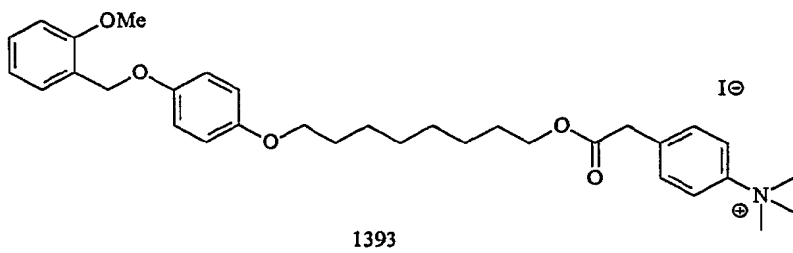
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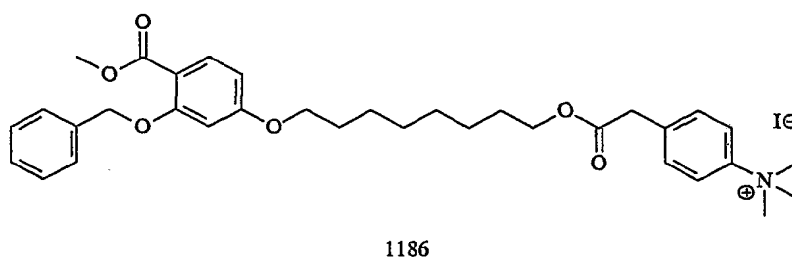
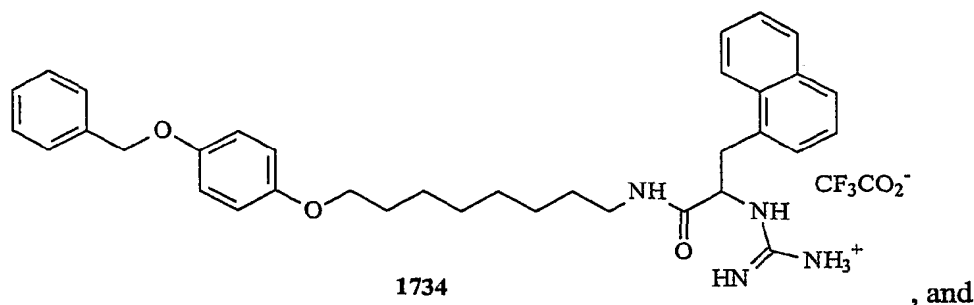
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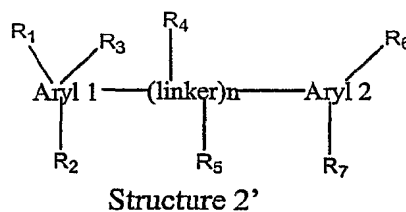


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wherein Γ is a pharmaceutically acceptable anion.

5 In a preferred embodiment, the inhibitor of NAD synthetase has the Structure 2':



wherein Aryl 1 is indolyl or phenyl; Aryl 2 is phenyl, pyridinyl, indolyl, or quinolinyl; and the linker is $-(CH_2)_n-$, $-(CH_2)_n-O-C(=O)-$, $-O(CH_2)_n-O-C(=O)-$, $-(CH_2)_n-O-C(=O)CH_2-$, or $-O(CH_2)_n-O-C(=O)CH_2-$.

For example, in Structures 2, 2', and 4, R₁-R₃ are independently selected from the group consisting of H, aryloxy, hydroxyaryl, aryl C₁-C₆ alkoxy, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, C₁-C₆ alkyl, C₁-C₆ alkyl carbonyl, aryl carbonyl, nitro, halo, carboxy, halo C₁-C₆ alkyl, perhalo C₁-C₆ alkyl, triphenylmethoxy, phenyl carbonyl amino, C₁-C₆ alkoxy carbonyl C₂-C₆ alkenyl, aryl carbonyl C₂-C₆ alkenyl, benzofuranyl carbonyl, C₁-C₆ alkyl benzyl furanyl carbonyl, aryl amino carbonyl, aryl carbonyloxy, amino carbonyl, C₁-C₆ alkoxy carbonyl amino, phthalidimido, morpholino, pyrrolidinyl, phenyl hydantoinyl, and acetyl piperazinyl; and R₆-R₇ are independently selected from the group consisting of H, C₁-

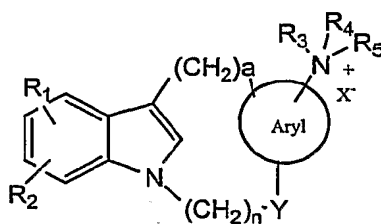
C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylammonium, C₁-C₆ N-alkyl, and C₁-C₆ alkoxy carbonyl. In an embodiment, R₃-R₄ are independently H.

In some embodiments, Aryl 1 is indolyl. In some other embodiments, Aryl 1 is phenyl. In certain embodiments, Aryl 2 is phenyl. In certain other embodiments, Aryl 2 is pyridinyl. In further embodiments, Aryl 2 is quinolinyl. In other embodiments, Aryl 2 is indolyl.

In certain embodiments, particularly where Aryl 1 is indolyl or phenyl, more particularly indolyl, R₁-R₃ are independently selected from the group consisting of H, phenoxy, hydroxyphenyl, benzyloxy, methoxy, methoxycarbonyl, isopropyl, butyl, acetyl, phenylcarbonyl, nitro, fluoro, carboxy, trifluoromethyl, triphenylmethoxy, phenylcarbonylamino, methoxycarbonyl ethenyl, phenylcarbonyl ethenyl, benzofuranyl carbonyl, butylbenzylfuranyl carbonyl, phenylaminocarbonyl, phenylcarbonyloxy, aminocarbonyl, methoxycarbonylamino, phthalidimido, morpholino, pyrrolidinyl, phenylhydantoinyl, and acetylpiperazinyl.

In other embodiments, particularly where Aryl 1 is phenyl, R₁-R₃ are independently selected from the group consisting of H, phenoxy, hydroxyphenyl, benzyloxy, acetyl, phenylcarbonyl, nitro, phenylcarbonyl ethenyl, benzofuranyl carbonyl, butylbenzylfuranyl carbonyl, phenylaminocarbonyl, phenylcarbonyloxy, aminocarbonyl, and methoxycarbonylamino.

Other examples of inhibitors of NAD synthetase has the Structure 300:

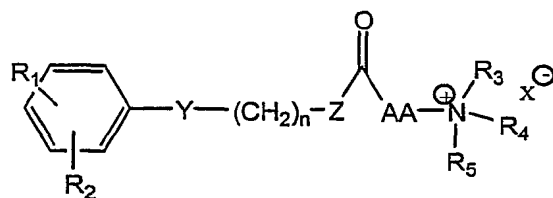


Structure 300

wherein Y is C, N, O, S, ester, amide, or ketone, n is an integer of from 1 to 12, a is an integer from 1-3, and R₁-R₅ each, independently, is H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, or an alkyl, alkenyl, or alkynyl, or an aryl group.

A further example of the inhibitor of NAD synthetase has the Structure 400:

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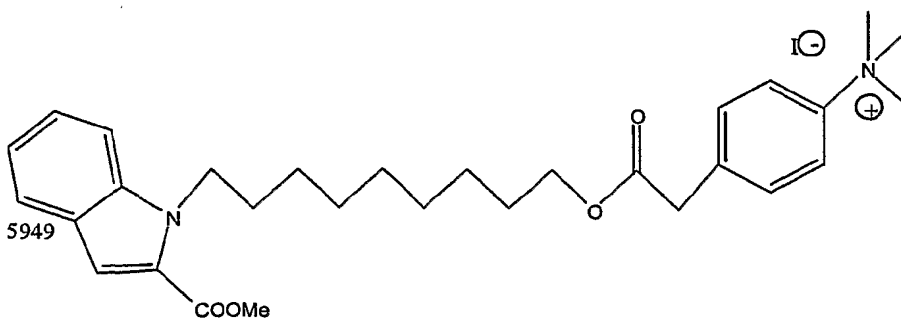
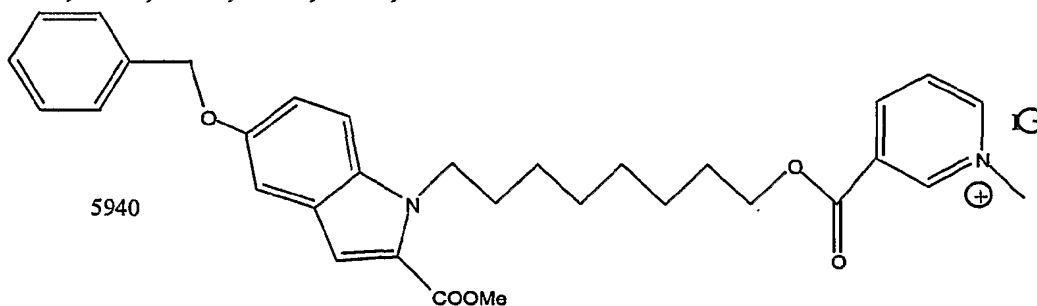


Structure 400

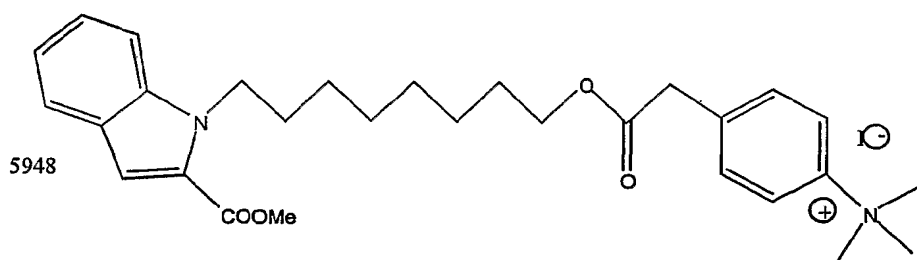
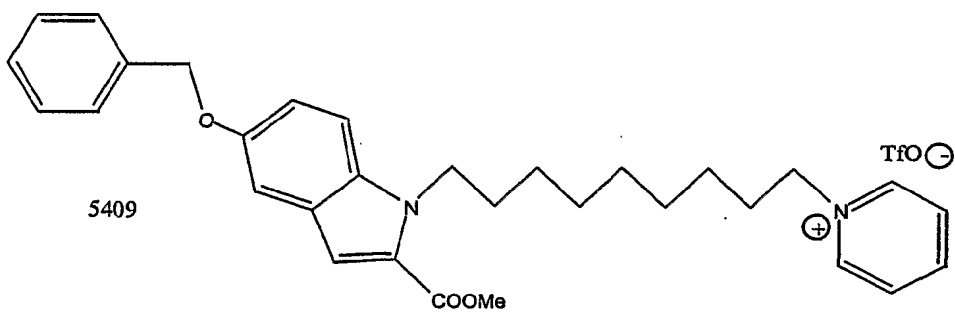
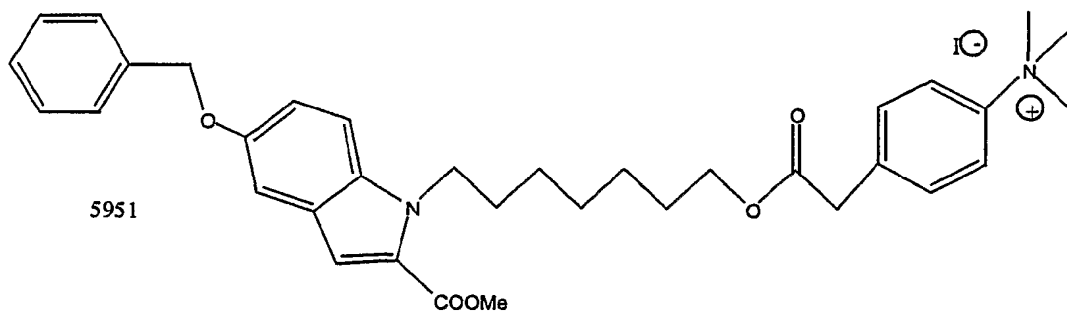
wherein Y is C, N, O, S, ester, amide, or ketone; Z is C, N, O, or S; AA is a natural or unnatural stereoisomer of an α -, β -, γ -, or δ -amino acid in which the carboxyl carbonyl is attached to Z, and the amino grouping may be a primary, secondary, tertiary, or quaternary ammonium compound; n is an integer of from 1 to 12; and R_1 - R_5 each, independently, is H, unsubstituted or substituted cyclic group or an aliphatic group, a branched or an unbranched group, or an alkyl, alkenyl, alkynyl, aryl, aryl alkyl, or aryl alkoxy group.

In Structures 300 and 400, R_1 - R_2 may also be H, hydroxyl, ketone, nitro, amino, amidino, guanidino, carboxylate, amide, ester, sulfonate, halogen, alkoxy, or aryloxy group.

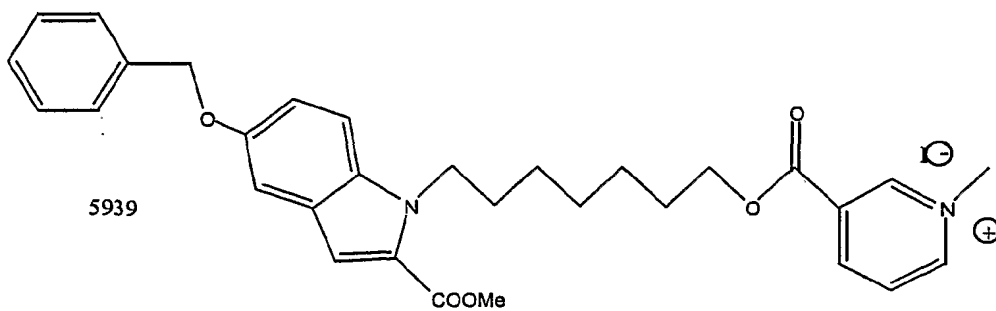
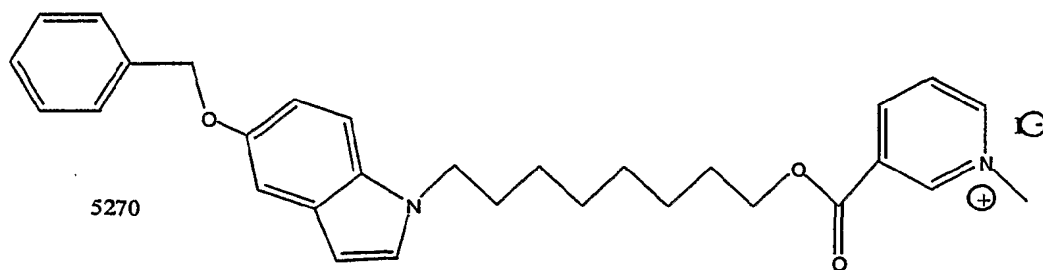
Particular examples of inhibitors of NAD synthetase are 5940, 5949, 5951, 5409, 5948, 5270, 5939, 5947, 5953, and 5274:



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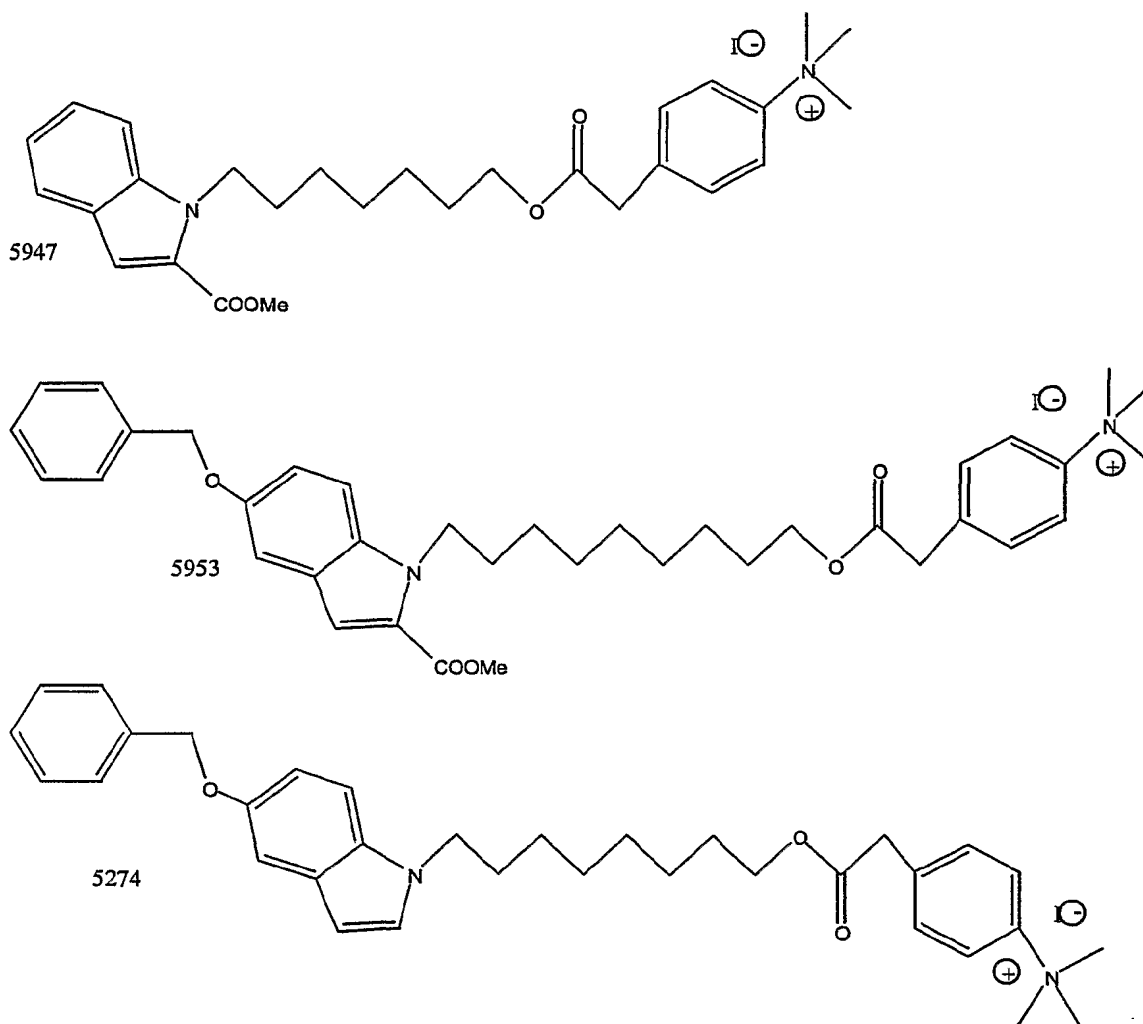


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The present invention further provides a method for treating or preventing a microbial (e.g., bacterial or fungal) infection in a mammal comprising administering to said mammal an effective amount of a compound that binds to the dimer interface of the NAD synthetase enzyme of the microbe (bacterium or fungus).

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In the method of killing yeast, as well as in the method of decreasing the growth of yeast, the NAD synthetase enzyme inhibitor is a compound that selectively binds with catalytic sites or subsites on a yeast NAD synthetase enzyme to reduce or eliminate the production of NAD by the yeast. In such methods, it is particularly preferably that there is little or no inhibitory activity on the host cell. For example, when the method is utilized to inhibit yeast activity in a mammal, it is preferred that there is little or no attendant affect on

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the NAD synthetase activity of the host. In one embodiment, the host is a mammal. In a further embodiment, the host is a plant.

In one embodiment, the invention provides administering an antifungal agent to a mammal in need of such treatment or prevention. In one embodiment, the fungal agent that causes the infection is yeast. In separate embodiments of the methods of administering, the antifungal agent comprises one or more compounds disclosed herein.

Further provided by the invention herein is preferably a method of killing yeast with an amount of yeast NAD synthetase enzyme inhibitor compound to reduce or eliminate the production of NAD whereby the yeast is killed. The present invention further provides a method of decreasing yeast growth, comprising contacting the yeast with an amount of yeast NAD synthetase enzyme inhibitor effective to reduce or eliminate the production of NAD whereby yeast growth is decreased is also provided.

The present invention provides, in an embodiment, a method for increasing production of a food animal comprising administering to the food animal an effective amount of at least one inhibitor of NADs of a microbe capable of infecting the food animal.

In another embodiment, the present invention provides a method for the treatment or prevention of infection by a spore-forming bacterium in an animal comprising treating an environment of the animal with an effective amount of at least one inhibitor of NADs of the spore-forming bacterium. In a further embodiment, the present invention provides a method for killing the vegetative cell of a spore-forming bacterium in an environment comprising treating the environment with an effective amount of at least one inhibitor of NADs of the bacterium. An example of a spore-forming bacterium is a biological warfare agent, e.g., *Bacillus anthracis*.

In still another embodiment, the present invention provides a method for treating a fungal or bacterial disease in a plant comprising treating the plant or an environment of the plant with an effective amount of at least one inhibitor of NADs of the fungus or bacterium. In a further embodiment, the present invention provides a method for a treating plant comprising the treating the plant, or an environment thereof, with a pesticidal effective amount of at least one inhibitor of NADs of a pest. An example of the plant is a food crop.

In yet another embodiment, the present invention provides a method for disinfecting, sterilizing, or decontaminating an object comprising treating the object with an effective

amount of at least one inhibitor of NADs of a microbe. The microbe is a microorganism, e.g., bacterium or fungus. An example of a fungus is mold or yeast.

Any suitable object can be disinfected, sterilized, or decontaminated. Examples of suitable objects include an article of clothing, an animal, an organ of an animal, a structure,
5 an equipment, a furniture, an environment, a food crop, a chicken, a chicken skin, and an egg, e.g., egg shell. In accordance with the present invention, the environment being disinfected, sterilized, or decontaminated can be land, air, or water, or a combination thereof.

An example of the environment includes a medical environment. Thus, for example,
10 a medical device, medical equipment, hospital, or surgical room can be disinfected. Medical personnel also can be disinfected or decontaminated. In accordance with the present invention, medical devices such as implantable medical devices, e.g., catheters can be disinfected, sterilized, or decontaminated. Medical equipment such as a surgical
15 equipment may also be disinfected, sterilized, or decontaminated. Further, the organs of animals, including human, can be disinfected or decontaminated. An example of an organ is the digestive tract.

In a further embodiment, the present invention provides a method for controlling insect population in an environment comprising treating the environment with an effective amount of at least one inhibitor of NADs of the insect. Any suitable environment can be
20 treated. For example, a household environment or an agricultural environment can be treated.

For the treatment of food animals to increase production, the inhibitor or antimicrobial agent may be mixed with animal feed at a typical concentration of 1-500 mg per kg of feed. Alternatively, similar concentrations may be added to the animals' drinking
25 water. Further alternatively, the antimicrobial agent may be administered as an oral pill or may be injected, either intramuscularly or intravenously.

The method of the present invention in an embodiment is useful in the prophylaxis or therapy of biological warfare agents, including, but not limited to, the spore-forming bacterium such as *Bacillus anthracis* or a microorganism carrying the virulent gene of a
30 spore-forming bacteria such as *Bacillus anthracis*. In *Bacillus anthracis* and other spore-forming bacteria, NADs is required for outgrowth of the germinated spore. Since inhibitors of NADs also prevent vegetative growth, this represents two different points of attack on

the life cycle of these bacteria and should provide extremely effective prophylaxis and/or therapy.

In the treatment of plants, in a typical application, the antimicrobial agent in a suitable vehicle is sprayed onto growing plants to either prevent or treat fungal and/or bacterial diseases. Alternatively, application may be made by deposition of solutions or solid preparations on the soil near growing plants.

In an application of NADs inhibitors as pesticides for controlling pests and insects in the household and/or for agricultural uses, NADs inhibitors with pesticidal or insecticidal activities and in a suitable vehicle, e.g., organic or aqueous vehicle, are sprayed in areas of homes that are commonly treated with existing insecticidal preparations. In a typical agricultural application, the pesticidal or insecticidal agent in a suitable vehicle is sprayed onto growing plants to either prevent or treat infestation by insects. Alternatively, pesticidal or insecticidal application to plants may be made by deposition on the soil near growing plants.

In a typical application for disinfection, sterilization or decontamination of structural surfaces, a solution of the microbicidal compound in a suitable vehicle would be painted, sprayed, or soaked (by immersion into a solution) onto the surface of the object. For treatment of the soil or ground, a solution of the microbicidal agent in a suitable vehicle may be sprayed onto or soaked into the ground, or a solid form may be mixed with the soil. The microbicidal agent may also be added to contaminated water supplies in sufficient concentration (1-100 micromolar) to cause sterilization. In processing, handling, and packaging animal foods, such as eggs or chickens, a solution of the microbicidal compound in a suitable vehicle may be painted, sprayed, or soaked (by immersion into a solution) onto the surface of the food. Numerous related beneficial applications are possible, including decontamination of chicken skins, e.g., to reduce *Salmonella typhimurium*, egg shells (carriers of *Salmonella*), and disinfection of other foods.

In the field of sterilization, disinfecting and decontamination including, microbicidal concentrations of NADs inhibitors have the potential for use in a variety of situations benefiting from sterilization or decontamination, including the treatment of clothing, surfaces of structures, equipment, furniture, and natural environmental surfaces such as the ground and water supplies.

A typical application for disinfection of implantable devices would involve soaking the device in a solution of the microbicidal compound. Alternatively, the implantable device may be manufactured to contain a releasable or bioactive form of the microbicidal compound, either by mechanical entrapment in the polymeric material composing the surface of the device or by covalent chemical attachment to the polymeric material composing the surface of the device. For treatment of transplantable organs, the organ may be immersed in a solution of the microbicidal agent contained in a suitable vehicle. Whole body washing can be accomplished by thoroughly wiping the body with a solution of the microbicidal agent, or by immersion of the body in a suitable solution.

Control of dental caries and/or gum disease may be accomplished by washing of the oral cavity with a suitable solution of the microbicidal agent, or by incorporation into a toothpaste used in brushing the teeth.

Numerous medical applications and devices requiring disinfection or decontamination are possible such as pacemakers, defibrillators, artificial hearts or parts thereof, whole body washing of infected patients, treatment of transplantable organs for transplantation, decontamination of surgical rooms and surgical equipment, and control of dental caries or gum disease.

Decontamination associated with spore-forming bacteria such as *Bacillus anthracis*, inhibitors of germination may cause damage to the spore and should be bactericidal to the vegetative cell. Thus these inhibitors may be used to decontaminate a variety of environments including, but not limited to, environmental surfaces and drinking water.

In the treatment, prevention, or control of fungal and bacterial diseases in plants and foodcrops, the inhibitor can be carried in a suitable vehicle and sprayed onto the plants to either prevent or treat fungal and/or bacterial diseases. Alternatively, application may be made by deposition of solutions or solid preparations on the soil near growing plants.

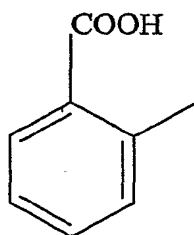
Numerous medical applications requiring disinfection or decontamination are possible. These include digestive tract decontamination in humans related to surgery (see G. Ramsay and R. H. van Saene, "Selective gut decontamination in intensive care and surgical practice: where are we [Review]," *World Journal of Surgery*, 22(2):164-70, Feb 1998; and G. Basha et al., "Local and systemic effects of intraoperative whole-colon washout with 5 per cent povidone-iodine," *British Journal of Surgery*. 86(2):219-26, Feb.

1999), the disinfection of, or impregnation of NADs inhibitors into, materials used in implantable devices such as intravenous catheters (see O. Traore et al., "Comparison of in-vivo antibacterial activity of two skin disinfection procedures for insertion of peripheral catheters: povidone iodine versus chlorhexidine," Journal of Hospital Infection. 44(2):147-50, Feb 2000; and T.S. Elliott, "Role of antimicrobial central venous catheters for the prevention of associated infections," [Review] Journal of antimicrobial Chemotherapy. 43(4):441-6, Apr. 1999), pacemakers, defibrillators, artificial hearts or parts thereof, whole body washing of infected patients, treatment of transplantable organs for transplantation, decontamination of surgical rooms and surgical equipment, and control of dental caries or gum disease (see B.M. Eley, "Antibacterial agents in the control of supragingival plaque--a review," British Dental Journal, 186(6):286-96, Mar 27 1999).

It is to be understood that this invention is not limited to the specific synthetic methods described herein. It is to be further understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment.

Throughout this application, where a chemical diagram has a straight line emanating from a chemical structure, such a line represents a CH₃ group. For example, in the following diagram:



o-methylbenzoic acid is represented.

The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, octyl, decyl, tetradecyl, hexadecyl, eicosyl, tetracosyl and the like.

5 The term "cycloalkyl" intends a cyclic alkyl group of from three to eight, preferably five or six carbon atoms.

The term "alkoxy" as used herein intends an alkyl group bound through a single, terminal ether linkage; that is, an "alkoxy" group may be defined as -OR where R is alkyl as defined above. A "lower alkoxy" group intends an alkoxy group containing from one to six,
10 more preferably from one to four, carbon atoms.

The term "alkylene" as used herein refers to a difunctional saturated branched or unbranched hydrocarbon chain containing from 1 to 24 carbon atoms, and includes, for example, methylene (-CH₂-), ethylene (-CH₂-CH₂-), propylene (-CH₂-CH₂-CH₂-), 2-methylpropylene [-CH₂-CH(CH₃)-CH₂-], hexylene [-(CH₂)₆-] and the like. The term
15 "cycloalkylene" as used herein refers to a cyclic alkylene group, typically a 5- or 6-membered ring.

The term "alkene" as used herein intends a mono-unsaturated or di-unsaturated hydrocarbon group of 2 to 24 carbon atoms. Asymmetric structures such as (AB)C=C(CD) are intended to include both the E and Z isomers. This may be presumed in structural
20 formulae herein wherein an asymmetric alkene is present.

The term "alkynyl" as used herein refers to a branched or unbranched unsaturated hydrocarbon group of 1 to 24 carbon atoms wherein the group has at least one triple bond.

The term "cyclic" as used herein intends a structure that is characterized by one or more closed rings. As further used herein, the cyclic compounds discussed herein may be
25 saturated or unsaturated and may be heterocyclic. By heterocyclic, it is meant a closed-ring structure, preferably of 5 or 6 members, in which one or more atoms in the ring is an element other than carbon, for example, sulfur, nitrogen, etc.

The term "bicyclic" as used herein intends a structure with two closed rings. As further used herein, the two rings in a bicyclic structure can be the same or different. Either
30 of the rings in a bicyclic structure may be heterocyclic.

By the term "effective amount" of a compound as provided herein is meant a sufficient amount of the compound to provide the desired treatment or preventive effect. As

will be pointed out below, the exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease that is being treated, the particular compound used, its mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate effective amount may be determined by one of ordinary skill in the art using only routine experimentation. It is preferred that the effective amount be essentially non-toxic to the subject, but it is contemplated that some toxicity will be acceptable in some circumstances where higher dosages are required.

By "pharmaceutically acceptable carrier" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the compounds of the invention without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

As used herein, "NAD synthetase enzyme" is defined as the enzyme that catalyzes the final reaction in the biosynthesis of NAD, namely, the transformation of NaAD into NAD. As used herein, the term "catalytic sites" are defined as those portions of the NAD synthetase enzyme that bind to substrates, and cofactors, including nicotinic acid dinucleotide (NaAD), NAD, adenosine triphosphate (ATP), adenosine monophosphate (AMP), pyrophosphate, magnesium and ammonia in bacteria or microbes. The term "receptor site" or "receptor subsite" relates to those portions of the bacterial NAD synthetase enzyme in which the bacterial NAD synthetase enzyme inhibitors disclosed herein are believed to bind. For the purposes of this disclosure, the terms "catalytic site," "receptor site" and "receptor subsite" may be used interchangeably. The inhibitors may also inhibit the NAD synthetase enzyme by mechanisms not involving binding of the inhibitor to catalytic sites.

As used herein, the term "antimicrobial compound" denotes a material that kills or deactivates microbes so as to reduce or eliminate the harmful effects of the bacteria on a subject or in a system. Microbes are microorganisms which are too small to be seen by the naked eye, e.g., bacteria, fungi, viruses, and protozoa, preferably bacteria and fungi. For example, antibacterials are known in the art as "bacteriostatic agents" or "bacteriocidal agents." The bacteria so affected can be gram positive, gram negative or a combination thereof. The terms "antimicrobial compound" and "broad spectrum antibiotic" denote a

material that kills or deactivates a wide variety of microbes, including, but not limited to, one of more of, gram positive or gram negative bacteria, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Enterococcus*, anaerobic *Streptococcus*, *Pneumococcus*, *Gonococcus*, *Meningococcus*, *Mima*, *Bacillus anthracis*, *C. diphtheriae*,
 5 *List. monocytogenes*, *Streptobacillus monohiliformis*, *Erysipelothrix insidiosa*, *E. coli*, *A. aerogenes*, *A. faecalis*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *K. pneumoniae*, *Salmonella*, *Shigella*, *H. influenzae*, *H. ducreyi*, *Brucella*, *Past. pestis*, *Past. tularensis*, *Past. multocida*, *V. comma*, *Actinobacillus mallei*, *Pseud. pseudomallei*, *Cl. tetani*, *Bacteroides*, *Fusobacterium fusiforme*, *M. tuberculosis*, atypical mycobacteria,
 10 *Actinomyces israelii*, *Nocardia*, *T. pallidum*, *T. pernu*, *Borrelia recurrentis*, *Peptospira*, *Rickettsia*, and *Mycoplasma pneumoniae*.

In accordance with the desirability for developing improved antimicrobials, e.g., antibacterial and antimicrobial agents, with the invention herein novel compounds have been identified that inhibit bacterial NAD synthetase enzymatic activity. Such activity
 15 translates into effectiveness as bacteriocidal agents, as well as effectiveness a broad spectrum antibiotic materials. Novel compounds have been developed that inhibit a previously unrecognized target in prokaryotic organisms, such as bacteria, to block essential biological function and thereby cause bacterial death or deactivation of the microbes. Specifically, the invention herein has identified an enzyme found in both gram positive and
 20 gram negative bacteria, NAD synthetase enzyme, which can be utilized as a target for drug design to provide protection from and/or treatment for bacterial and other microbial infections.

The NAD synthetase enzyme catalyzes the final step in the biosynthesis of nicotinamide adenine dinucleotide (NAD). Bacterial NAD synthetase is an ammonia-
 25 dependent amidotransferase belonging to a family of "N-type" ATP pyrophosphatases; this family also includes asparagine synthetase and argininosuccinate synthetase. NAD synthetase enzyme catalyzes the last step in both the *de novo* and salvage pathways for NAD⁺ biosynthesis, which involves the transfer of ammonia to the carboxylate of nicotinic acid adenine dinucleotide (NaAD) in the presence of ATP and Mg⁺². The overall reaction
 30 is illustrated in Fig. 1. Unlike eukaryotic NAD synthetase e.g., that found in mammals, which can utilize glutamine as a source of nitrogen, prokaryotic NAD synthetase in bacteria utilizes ammonia as the sole nitrogen source. Through x-ray crystallography and other

methods, the invention has identified marked differences in the structures of eukaryotic and prokaryotic forms of the NAD synthetase enzyme. For example, *B. subtilis* NAD synthetase enzyme, which in the invention has been crystallized and used in the drug design methodologies herein, is a dimeric material with molecular weight around 60,500. In marked contrast, the eukaryotic form of NAD synthetase found in mammals is multimeric and has a molecular weight of at least 10 times larger.

By utilizing the significant differences between the eukaryotic and prokaryotic forms of NAD synthetase enzyme, the invention herein provides novel compounds that can be utilized as antimicrobial agents that specifically target the prokaryotic NAD synthetase enzyme without significantly affecting a mammalian host. With the invention herein, it has been found that by specifically inhibiting bacterial NAD synthetase enzymatic activity, bacteria can be deprived of the energy necessary to thrive and replicate. Accordingly, through the invention disclosed and claimed herein, antibacterial drugs may be developed that preferentially attack the bacteria to kill or deactivate it so as to reduce or eliminate its harmful properties, without appreciably affecting mammalian NAD synthetase enzymatic activity at the same dosage. Moreover, the invention provides methods of treating microbial infections in a mammal, e.g., human. Because of the differences in structure between bacterial and mammalian NAD synthetase enzyme, it would not be expected that the compounds of the invention would inhibit or otherwise affect mammalian NAD synthetase enzyme in the same manner as the compounds act on bacteria.

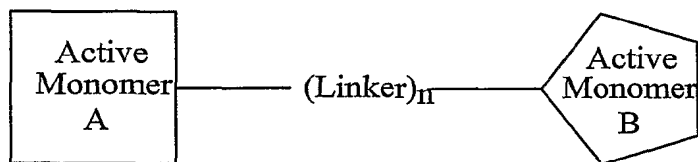
Without being bound by theory, through chemical analysis and x-ray crystallography methods, characterized at least two separate catalytic subsites on the bacterial NAD synthetase enzyme in which it is possible to bind at least one or more small molecules ("active molecules") have been characterized. These sites are illustrated in Figure 2.

Because of the specific structure of these catalytic sites, it may be possible to identify small molecules that will demonstrate affinity for at least one of the sites. Small molecules of the proper configuration, the configuration being determined by the structure of the catalytic site(s), may bind with a receptor site or sites on the microbial, e.g., bacterial NAD synthetase enzyme, thereby blocking the catalytic activity of the enzyme. Figure 3 illustrates a bacterial NAD synthetase enzyme in which the catalytic sites are blocked by an example of a compound of the present invention.

Under such circumstances, it is hypothesized that, for example, spore-forming bacteria will be unable to undergo germination and outgrowth, and the essential cellular respiratory functions of the vegetative bacteria will be halted, thereby causing cellular death or deactivation, *e.g.*, gram positive and gram negative bacteria and other microbes will be killed or prevented from growing. Accordingly, the invention has found that compounds that exhibit inhibitory activity against the bacterial NAD synthetase enzyme will also exhibit therapeutic activity as antibacterial and antimicrobial compounds, as well as broad spectrum antibiotic materials.

With embodiments of the invention described herein, it is possible to synthesize novel tethered dimeric compounds that exhibit activity as microbial NAD synthetase enzyme inhibitors. By linking one or more active molecules through a linker molecule, one or more ends of the tethered dimer can bind in the respective receptor sites or subsites to thereby render the bacterial NAD synthetase enzyme inactive. When more than one active molecule is used, each active molecule can be the same or different. The term “active molecules” as used herein refers to small molecules that may be used alone or tethered together through a linker (tether) fragment to form a tethered dimeric compound.

Further, under some circumstances, different active molecules will be more likely to bind to different locations in the receptor site of a bacterial NAD synthetase enzyme because of the differing chemical make-up of each of these sites. Therefore, in one embodiment, it may be beneficial to tether at least two different active molecules to each other wherein each active molecule demonstrates selective affinity for a different subsite in the receptor. Using the tethered dimers herein it may be possible to drastically enhance the potency of NAD synthetase enzyme inhibition, as compared to blocking a single site on the bacterial NAD synthetase enzyme. As used herein, the term “selective affinity” means that the active molecule shows enhanced tendency to bind with one subsite with the receptor in the bacterial NAD synthetase enzyme because of a chemical complementarity between the receptor subsite and the active molecule. A tethered dimer compound is illustrated below.



In one embodiment, a dimeric inhibitor compound will bind with, for example, the sites of catalytic activity on the bacterial NAD synthetase enzyme, thereby preventing the production of NAD/NADH by the bacteria. By varying the length of the linker molecule, or the distance between the two active molecules, the affinity of the inhibitor compound for the NAD synthetase enzyme may be varied.

In practice of the invention relating to the design of novel NAD synthetase enzyme inhibitor compounds, a software program can be utilized which facilitates the prediction of the binding affinities of molecules to proteins so as to allow identification of commercially available small molecules with the ability to bind to at least one receptor subsite in the bacterial NAD synthetase enzyme. An example of one such computer program is DOCK, available from the Department of Pharmaceutical Chemistry at the University of California, San Francisco. DOCK evaluates the chemical and geometric complementarity between a small molecule and a macromolecular binding site.

The active molecules specifically disclosed herein may be used, as well as any pharmaceutically acceptable salts thereof. As noted, pharmaceutically acceptable salts of the compounds set out herein below are also contemplated for use in this invention. Such salts are prepared by treating the free acid with an appropriate amount of a pharmaceutically acceptable base. Representative pharmaceutically acceptable bases are ammonium hydroxide, sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide, ferrous hydroxide, zinc hydroxide, copper hydroxide, aluminum hydroxide, ferric hydroxide, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, histidine, and the like. The reaction is conducted in water, alone or in combination with an inert, water-miscible organic solvent, at a temperature of from about 0°C to about 100°C, preferably at room temperature. The molar ratio of the compounds to base used are chosen to provide the ratio desired for any particular salts. For preparing, for example, the

ammonium salts of the free acid starting material—a particular preferred embodiment—the starting material can be treated with approximately one equivalent of pharmaceutically acceptable base to yield a neutral salt. When calcium salts are prepared, approximately one-half a molar equivalent of base is used to yield a neutral salt, while for aluminum salts,
5 approximately one-third a molar equivalent of base will be used.

Compounds prepared in accordance with the design and synthesis methods of this invention are especially attractive because they may preferably be further optimized by incorporation of substituents on either the active molecule and/or the linking group. These latter modifications can also preferably be accomplished using the combinatorial methods
10 disclosed herein.

In a preferred embodiment, the invention provides administering a broad spectrum antibiotic to a mammal in need of such treatment or prevention. In a further preferred embodiment, the microbial infection is a bacterial infection. In yet another embodiment of the invention, the bacterial infection is caused by a bacterium that is a gram negative or
15 gram positive bacteria. The bacterial infection may preferably be caused by an antibiotic resistant strain of bacteria.

Further provided by the invention herein is preferably a method of killing a prokaryote with an amount of prokaryotic NAD synthetase enzyme inhibitor compound to reduce or eliminate the production of NAD whereby the prokaryote is killed. A method of
20 decreasing prokaryotic growth, comprising contacting the prokaryote with an amount of a prokaryotic NAD synthetase enzyme inhibitor effective to reduce or eliminate the production of NAD whereby prokaryotic growth is decreased is also provided. In the method of killing a prokaryote, as well as in the method of decreasing prokaryotic growth, the compound comprises one or more compounds provided herein.

25 In the method of killing a prokaryote, as well as in the method of decreasing prokaryotic growth, the prokaryote is a bacterium. Further preferably, the bacterium is a gram negative or a gram positive bacteria. Still preferably, the prokaryote is an antibiotic resistant strain of bacteria.

Also in the method of killing a prokaryote, as well as in the method of decreasing
30 prokaryotic growth, the NAD synthetase enzyme inhibitor is a compound that selectively binds with catalytic sites or subsites on a bacterial NAD synthetase enzyme to reduce or eliminate the production of NAD by the bacteria.

In the methods discussed above, the compound is preferably administered by oral, rectal, intramuscular, intravenous, intravesicular or topical means of administration. The compounds of this invention can be administered to a cell of a subject either *in vivo* or *ex vivo*. For administration to a cell of the subject *in vivo*, as well as for administration to the
5 subject, the compounds of this invention can be administered orally, parenterally (*e.g.*, intravenously), by intramuscular injection, by intraperitoneal injection, subcutaneous injection, transdermally, extracorporeally, topically, mucosally or the like.

Depending on the intended mode of administration, the compounds of the present invention can be in pharmaceutical compositions in the form of solid, semi-solid or liquid
10 dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, gels, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include, as noted above, an effective amount of the selected composition, possibly in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents,
15 pharmaceutical agents, carriers, adjuvants, diluents, etc.

Parenteral administration of the compounds of the present invention, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. As used herein, "parenteral administration"
20 includes intradermal, subcutaneous, intramuscular, intraperitoneal, intravenous and intratracheal routes. One approach for parenteral administration involves use of a slow release or sustained release system such that a constant dosage is maintained. These compounds can be present in a pharmaceutically acceptable carrier, which can also include a suitable adjuvant. By "pharmaceutically acceptable," it is meant a material that is not
25 biologically or otherwise undesirable, *i.e.*, the material may be administered to an individual along with the selected compound without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained.

Routes of administration for the compounds herein are preferably in a suitable and
30 pharmacologically acceptable formulation. When administered to a human or an animal subject, the bacterial NAD synthetase enzyme inhibitor compounds of the libraries herein are preferably presented to animals or humans orally, rectally, intramuscularly,

intravenously, intravesicularly or topically (including inhalation). The dosage preferably comprises between about 0.1 to about 15g per day and wherein the dosage is administered from about 1 to about 4 times per day. The preferred dosage may also comprise between 0.001 and 1 g per day, still preferably about 0.01, 0.05, 0.1, and 0.25, 0.5, 0.75 and 1.0 g per day. Further preferably, the dosage may be administered in an amount of about 1, 2.5, 5.0, 7.5, 10.0, 12.5 and 15.0 g per day. The dosage may be administered at a still preferable rate of about 1, 2, 3, 4 or more times per day. Further, in some circumstances, it may be preferable to administer the compound of the invention continuously, as with, for example, intravenous administration. The exact amount of the compound required will vary from subject to subject, depending on the species, age, weight and general condition of the subject, the particular compound used, its mode of administration and the like. Thus, it is not possible to specify an exact amount for every compound. However, an appropriate amount can be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein.

If *ex vivo* methods are employed, cells or tissues can be removed and maintained outside the subject's body according to standard protocols well known in the art. The compounds of this invention can be introduced into the cells via known mechanisms for uptake of small molecules into cells (*e.g.*, phagocytosis, pulsing onto class I MHC-expressing cells, liposomes, etc.). The cells can then be infused (*e.g.*, in a pharmaceutically acceptable carrier) or transplanted back into the subject per standard methods for the cell or tissue type. Standard methods are known for transplantation or infusion of various cells into a subject.

It is further provided a method of disinfecting a material contaminated by a microbe, comprising contacting a contaminated material with a bacterial NAD synthetase enzyme inhibitor compound in an amount sufficient to kill or deactivate the microbe. In yet another embodiment, the compound utilized for contacting comprises one or more compounds provided herein.

In yet a further embodiment of the invention herein, the compounds of the present invention are effective as disinfectant materials for, for example, hard or soft surfaces, fabrics, and other contaminated materials such as those in hospitals, households, schools, nurseries, and any other location. In yet another embodiment, the invention provides a

method for disinfecting comprising contacting a bacterial contaminated material with a bacterial NAD synthetase enzyme inhibitor compound.

The inhibitors of NAD synthetase according to the present invention can be employed in a variety of processes for the treatment of humans, animals and plants as well as decontamination, sterilization and/or disinfectant techniques. The present invention further provides a method for preventing germination of spore-forming bacteria and/or the vegetative growth of bacteria, fungi and/or molds comprising administering an effective amount of at least one inhibitor of NAD synthetase, e.g. prophylactically or therapeutically, e.g., to at least one of a human, a mammal, or an animal.

The present invention further provides a method for preparing a compound of the formula A:



wherein Ar₁, Ar₂, and Ar₃ are independently aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and heterocyclyl; optionally, a ring nitrogen atom of heteroaryl Ar₁, Ar₂, or Ar₃ may be quaternized;

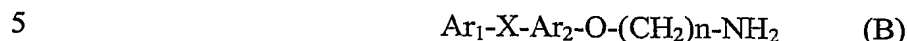
X is selected from the group consisting of a covalent bond, (CH₂)_mO, O(CH₂)_m, (CH₂O)_m, (OCH₂)_m, (CH₂CH₂O)_m, (OCH₂CH₂)_m, C(=O)O, OC(=O), OC(=O)O, (CH₂)_mS, S(CH₂)_m, (CH₂S)_m, (SCH₂)_m, NH, NR, ⁺NR₂, C(=O)NH, C(=O)NR, NHC(=O), NRC(=O), CH(OH), and CH(OR), wherein R is C₁-C₆ alkyl and m is 0-5;

Q₁ is (i) a C₁-C₆ alkylenyl, C₁-C₆ alkylenyl carbonyloxy C₁-C₆ alkyl, or C₁-C₆ alkylenyl carbonylamino C₁-C₆ alkyl group, optionally having a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, C₁-C₆ haloalkylamino, C₁-C₆ haloalkyl C₁-C₆ alkyl amino, C₁-C₆ hydroxyalkylamino, C₁-C₆ hydroxyalkyl C₁-C₆ alkylamino, C₁-C₆

dialkylamino, C₁-C₆ trialkylamino, and a heterocyclic containing a nitrogen atom which may be optionally quaternized;

and n is from 1 to 15;

comprising (i) providing a compound of the formula B:

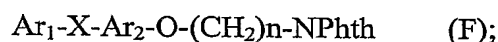


and (ii) reacting the compound of formula B with a compound of formula C:



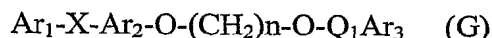
wherein Q₁ is optionally protected.

10 In an embodiment, the compound of formula B may be prepared by reacting a compound of formula D: Ar₁-X-Ar₂-OH (D) with a compound of formula E: Hal-(CH₂)_n-NPhth (E); wherein "Hal" stands for a halogen atom and "NPhth" stands for phthalidimide linked to (CH₂)_n at the nitrogen atom, to obtain a compound of formula F:



and hydrolyzing the compound of formula F.

15 In accordance with another embodiment, the present invention provides a method for preparing a compound of the formula G:



wherein Ar₁, Ar₂, and Ar₃ are independently aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ 20 alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ 25 alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and heterocyclyl; optionally, a ring nitrogen atom of heteroaryl Ar₁, Ar₂, or Ar₃ may be quaternized;

30 X is selected from the group consisting of a covalent bond, (CH₂)_mO, O(CH₂)_m, (CH₂O)_m, (OCH₂)_m, (CH₂CH₂O)_m, (OCH₂CH₂)_m, C(=O)O, OC(=O), OC(=O)O, (CH₂)_mS, S(CH₂)_m, (CH₂S)_m, (SCH₂)_m, NH, NR, ⁺NR₂, C(=O)NH, C(=O)NR, NHC(=O), NRC(=O), CH(OH), and CH(OR), wherein R is C₁-C₆ alkyl and m is 0-5;

Q₁ is (i) a C₁-C₆ alkylenyl, C₁-C₆ alkylenyl carbonyloxy C₁-C₆ alkyl, or C₁-C₆ alkylenyl carbonylamino C₁-C₆ alkyl group, optionally having a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, C₁-C₆ haloalkylamino, C₁-C₆ haloalkyl C₁-C₆ alkyl amino, C₁-C₆ hydroxyalkylamino, C₁-C₆ hydroxyalkyl C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, and a heterocyclic containing a nitrogen atom which may be optionally quaternized;

and n is from 1 to 15;

comprising (i) providing a compound of the formula H:



and (ii) reacting the compound of formula H with a compound of formula J:

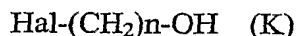


wherein Q₁ is optionally protected.

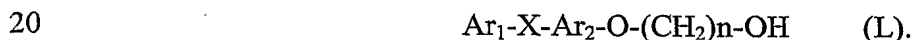
In accordance with an embodiment, the compound of formula H may be prepared by reacting a compound of formula D:



with a compound of formula K:



wherein "Hal" stands for a halogen atom, e.g., cl, Br, or I to obtain a compound of formula L:



In a preferred embodiment, the present invention provides a method for preparing the above compounds wherein n is from 7 to 13 relating to compounds of formulas A and G. In accordance with an embodiment, Ar₁, Ar₂, and Ar₃ are aryl, particularly phenyl. In an embodiment, X is CH₂O. In accordance with an embodiment of the method, Q₁ is a C₁-C₆ alkylenyl, optionally having a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, C₁-C₆ haloalkylamino, C₁-C₆ haloalkyl C₁-C₆ alkyl amino, C₁-C₆ hydroxyalkylamino, C₁-C₆ hydroxyalkyl C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, and a heterocyclic containing a nitrogen atom which may be optionally quaternized, preferably Q₁ is C₁-C₃ alkylenyl, having a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, and C₁-C₆ trialkylamino.

The present invention further provides a pharmaceutical composition comprising at least one of the compounds described along with a pharmaceutically acceptable carrier.

The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, or diluents, are well-known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active compound and one which has no detrimental side effects or toxicity under the conditions of use.

The choice of carrier will be determined in part by the particular active agent, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intraarterial, intramuscular, interperitoneal, intrathecal, rectal, and vaginal administration are merely exemplary and are in no way limiting.

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols and polyethylene glycols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and cornstarch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These

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such formulations. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

The compounds of the present invention may be made into injectable formulations. The requirements for effective pharmaceutical carriers for injectable compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J.B. Lippincott Co., Philadelphia, PA, Banker and Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986).

The present invention further provides a method for treating or preventing a microbial (e.g., bacterial or fungal) infection in a mammal comprising administering to said mammal an effective amount of at least one of the compounds described above. The present invention also provides a method for treating or preventing tuberculosis.

The present invention further provides a method for combating agroterrorism involving an infective agent on an object comprising treating the object with an amount of a compound effective to inhibit the NAD synthetase of the infective agent. Agroterrorism is defined as the intentional introduction of animal or plant pests or the cultivation or production of pathogenic bacteria, fungi, parasites, protozoans, viruses, or their toxic products for the purpose of causing poultry, livestock, crop, soil, or human disease, poisoning, or death. This could occur through introducing pests intended to kill food crops, spreading virulent disease among confined feedlots where animals are given high protein rations for preparing them for slaughter, poisoning civil or agricultural water sources or food supplies, or using food-borne pathogens to cause human disease. Food-borne pathogens are microorganisms that cause illness through the ingestion of food.

The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

5

This Example illustrates a method of preparing compounds of the present invention in accordance with an embodiment of the invention.

Experimental Procedures

Melting points were determined using an Electrothermal 9100 apparatus and are
10 uncorrected. IR spectra were taken with Brucker Vector-22 and Bomem MB-104
instruments. All ^1H and ^{13}C NMR spectra were recorded on a Brucker 300 MHz
spectrometer using TMS as internal standard. The values of chemical shifts (δ) are given in
ppm and coupling constants (J) in Hz. Elemental analyses were performed by Atlantic
Microlab, Norcross, Georgia. Reactions were monitored by TLC (Whatmann, Silica gel,
15 UV254, 25 μM plates) and flash column chromatography was done using 'BAKER' silica
gel (40 μM) in solvent systems indicated. The solvents used for reactions were purchased as
anhydrous in Sure-SealTM bottles from Aldrich chemical company. All other reagents were
used as received.

20 Synthesis of compound 1364 (Scheme 1)

Compound 2

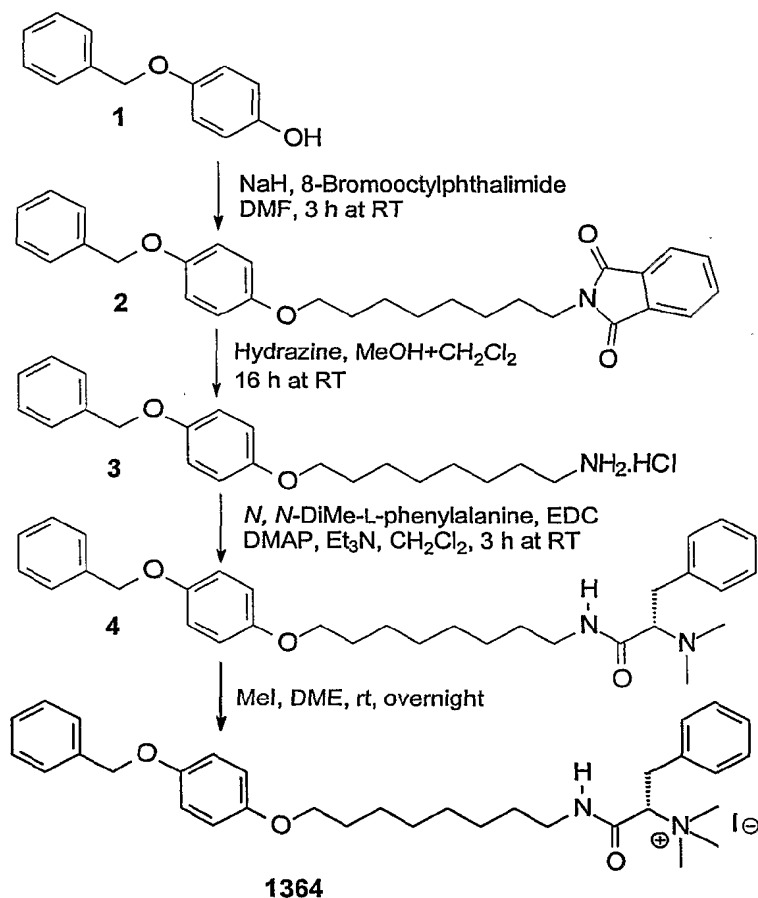
To a solution of 4-(benzyloxy)phenol **1** (0.40g, 2.0mmol) in 10mL of DMF was added
solid NaH (60% in mineral oil, 88 mg, 2.2mmol), and the mixture was stirred at r.t for 30
min under a nitrogen atmosphere. N-(8-Bromooctyl) phthalimide (0.74g, 2.2mmol) was
25 added and the mixture stirred at room temperature for 3h. The reaction mixture was
quenched with water (20mL) and extracted with EtOAc (2x20mL). The organic layer was
washed with water (2x10mL) and brine (10mL), Removal of solvent from the dried
(Na_2SO_4) extract gave the crude product. It was crystallized from MeOH to afford **2** (0.71g,
78% yield) as a white solid. m.p: 74-75°C (MeOH)., ^1H -NMR (CDCl_3) δ 1.26-1.48 (m, 8H),
30 1.59-1.79 (m, 4H), 3.67 (t, 2H, J=7.28Hz), 3.88 (t, 2H, J=6.53Hz), 5.00 (s, 2H), 6.81 (d, 2H,
J=9.14Hz), 6.89 (d, 2H, J=9.15Hz), 7.27-7.45 (m, 5H), 7.66-7.73 (m, 2H) and 7.81-7.86 (m,
2H); ^{13}C NMR (CDCl_3) δ 25.9, 26.7, 28.5, 29.1, 29.2, 29.3, 37.9, 68.4, 70.6, 115.3, 115.7,

123.1, 127.4, 127.8, 128.5, 132.1, 133.8, 137.3, 152.7, 153.4 and 168.4; IR (neat): 1693 cm^{-1} ; MS (ES^+): 458 ($\text{M}+1$).

Compound 3

5 To a solution of **2** (11.1g, 24.3mmol) in CH_2Cl_2 (120mL) and MeOH (16mL) was added anhydrous hydrazine (2.29mL, 72.9mmol) at r.t. under a nitrogen atmosphere. The reaction mixture was stirred overnight at r.t. Formation of white precipitate, which is a by-product occurred. The precipitate was filtered and washed with NH_4OH saturated CHCl_3 :MeOH (10:1). The filtrate was evaporated to get rid of methanol, then re-dissolved in NH_4OH
10 saturated CHCl_3 (400mL), washed with 1N NaOH (3x60mL), water (2x60mL), and brine (2x60mL). After drying over Na_2SO_4 , the organic layer was concentrated to about 250mL, and 1N HCl (60mL) was added to the above solution, resulting in the formation of a white precipitate. This was filtered and washed with water and CHCl_3 . After drying under vacuum hydrochloride salt **3** (6.8g, 77% yield) was obtained as a white solid., m.p. 180-
15 182°C, ^1H -NMR (DMSO-d_6) δ 1.22-1.44 (m, 8H), 1.48-1.61 (m, 2H), 1.61-1.72 (m, 2H), 2.67-2.81 (m, 2H), 3.86 (t, 2H, $J=6.38\text{Hz}$), 5.02 (s, 2H), 6.83 (d, 2H, $J=9.10\text{Hz}$), 6.92 (d, 2H, $J=9.09\text{Hz}$), 7.28-7.45 (m, 5H) and 7.98 (bs 3H); ^{13}C NMR (CDCl_3) δ 25.5, 25.8, 26.9(2C), 28.5, 28.6, 28.8, 67.7, 69.6, 115.2, 115.6, 127.6, 127.7, 128.4, 137.4, 152.2 and 152.8; IR (neat): 3440 cm^{-1} ; MS (ES^+): 328 (M^+).

Scheme 1

5 **Compound 4**

Compound 3 (hydrochloride salt) (0.95g, 2.6mmol) was suspended in CH₂Cl₂ (15mL) and cooled to 0°C. Et₃N (0.44mL, 3.12mmol) was added and stirred for 5min. Then *N,N*-dimethyl-L-phenylalanine (0.61g, 3.12mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (0.60g, 3.12mmol) and DMAP (0.036g, 0.3mmol) were added. The reaction mixture was stirred at r.t. overnight. The reaction mixture was diluted with CH₂Cl₂ (50mL) and washed with 1M NaHCO₃ (2x20mL), water (2x20mL), and brine (20mL). Removal of solvent from the dried (Na₂SO₄) extract gave the crude product, which was purified by flash column chromatography (20x4cm) over silica gel using 1% MeOH in CHCl₃ to afford the pure amide 4 (1.35g, 103 % yield) as a white solid., mp: 61-62°C, ¹H-

NMR (CDCl₃) δ 1.18-1.35 (m, 6H), 1.35-1.49 (m, 4H), 1.67-1.81 (m, 2H), 2.29 (s, 6H), 2.81-2.92 (m, 1H), 3.08-3.26 (m, 4H), 3.88 (t, 2H, J=6.52Hz), 4.99 (s, 2H), 6.73 (bs, 1H), 6.81 (d, 2H, J=9.17Hz), 6.89 (d, 2H, J=9.18Hz) and 7.12-7.45 (m, 10H); ¹³CNMR (CDCl₃) δ 25.8, 26.7, 29.1, 29.2, 29.3, 29.5, 32.7, 38.9, 42.2, 68.4, 70.5, 71.0, 115.2, 115.6, 125.9, 127.3, 127.7, 128.2, 128.4, 129.1, 137.2, 140.0, 152.7, 153.4 and 171.9; MS (ES⁺): 503 (M+1); Anal. Calcd for C₃₂H₄₂N₂O₃·0.5H₂O: C, 75.16; H, 8.47; N 5.48, found: C, 75.15; H, 8.23 and N 5.42.

Compound 1364

To a solution of compound 4 (0.096g, 0.19 mmol) in anhydrous DME (3mL) was added iodomethane (0.35 mL, 5.6 mmol). The reaction mixture was heated at 80°C for 12 h with stirring and cooled to room temperature. After evaporation, the crude product was purified by flash silica gel column (10x2cm) chromatography over silica gel using, stepwise, CHCl₃ : MeOH (30:1 followed by 10:1) to afford pure 1364 (0.095g, 77% yield). m.p.: 98-99°C., ¹H-NMR (CDCl₃) δ 0.95-1.31 (m, 8H), 1.31-1.45 (m, 2H), 1.66-1.79 (m, 3H), 2.85-2.99 (m, 1H), 3.03-3.15 (m, 1H), 3.15-3.33 (m, 2H), 3.48 (s, 9H), 3.88 (t, 3H, J=6.52Hz), 5.00 (s, 2H), 5.74 (dd, 1H, J₁=11.2Hz, J₂=4.57Hz), 6.83 (d, 2H, J=9.17Hz), 6.90 (d, 2H, J=9.17Hz), 7.22-7.43 (m, 10H) and 7.78 (t, 1H, J=5.58Hz); ¹³CNMR (CDCl₃) δ 20; IR (neat): 3245, 1679 cm⁻¹; MS (ES⁺): 517(M⁺); Anal. Calcd for C₃₃H₄₅N₂O₃: C, 61.49; H, 7.04; N 4.35; found: C, 61.20; H, 6.89 and N, 4.23.

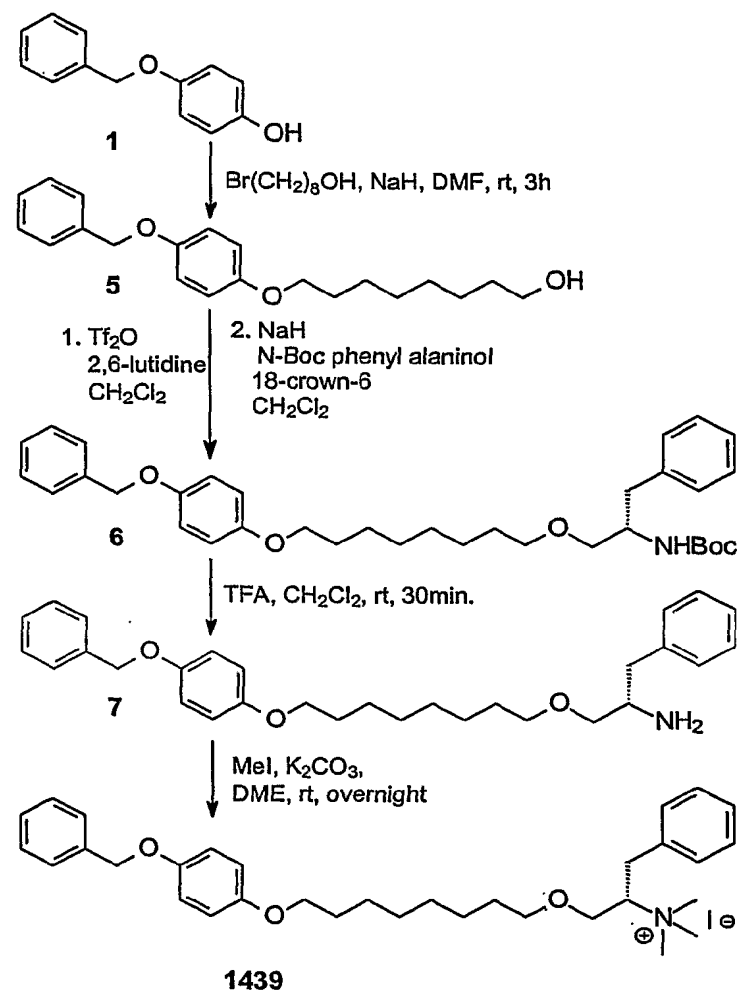
Synthesis of 1439 (Scheme 2)

Compound 5.

To a solution of 4-(benzyloxy)phenol 1 (2.4g, 12mmol) in DMF (32mL) was added sodium hydride (0.528g, 13.2mmol, 60% in mineral oil), and the mixture was stirred under N₂ at r.t. for 30 min. 8-Bromo-1-octanol (2.25mL, 13.2mmol) was added and the reaction mixture was further stirred at r.t. for 5h. TLC (30% EtOAc in hexanes) showed that reaction was complete. After being quenched with saturated ammonium chloride solution and ice, the mixture was extracted with EtOAc (3x60mL). The combined organic layer was then washed with 1N. NaOH solution (2x40mL), water (2x40mL) and brine (2x40mL). After drying (Na₂SO₄) the organic layer was evaporated and concentrated to around 20mL, when

a white solid began precipitating. The mixture was cooled, filtered, and the filter washed with hexane to give 2.2 g white solid. The filtrate was further cooled to give another 0.8 g of **5** (76.9% yield) as a white solid.,mp. 94-95°C. ¹H-NMR (CDCl₃) δ 1.28-1.51 (m, 8H), 1.51-1.63 (m, 3H), 1.69-1.81 (m, 2H), 3.62 (t, 2H, J=6.58Hz), 3.88 (t, 2H, J=6.52Hz), 5.00 (s, 2H), 6.82 (d, 2H, J=9.09Hz), 6.89 (d, 2H, J=9.21Hz) and 7.26-7.45(m, 5H); ¹³C-NMR (CDCl₃) δ 25.6, 25.9, 29.3, 32.6, 62.9, 68.5, 70.6, 115.3, 115.7, 127.4, 127.8, 128.4, 137.2, 152.7 and 153.4; IR (KBr): 3303 cm⁻¹; MS (ES⁺): 329 (M+1); Anal. Calcd for C₂₁H₂₈O₃: C, 76.78; H, 8.60; found: C, 76.64 and H, 8.58.

Scheme 2

Compound 6

- 5 To a cooled solution (0°C) of alcohol 5 (1g, .3.05mmol) in CH₂Cl₂ (40mL) was added 2,6-lutidine (0.46mL, 3.955mmol), followed by triflic anhydride (0.62mL, 3.687mmol). After stirred at 0°C for 15min. TLC (EtOAc:Hexanes 1:3) showed the reaction is complete. The reaction mixture was then washed with water (2x20mL), brine (20mL) and dried (Na₂SO₄). The solvent was completely removed and the product triflate was dried at high vacuum for
- 10 10 min. Triflate was then dissolved in CH₂Cl₂ (10mL) and added in 10 minutes to a solution

of N-Boc phenyl alaninol (1.53g, 6.095mmol) and NaH (0.305g, 60% in mineral oil, 7.625mmol) in CH₂Cl₂ (30mL) kept at 0°C. Reaction bubbled vigorously. It was stirred for 5 minutes and 18-crown-6 (0.081g, 0.307mmol) was added and the reaction mixture was allowed to attain room temperature and stirred at room temp for 30 minutes. TLC (25%EtOAc in hexanes) showed that the reaction is complete. Reaction was then washed with water (2x20mL) and brine (20mL). Removal of solvent from the dried (Na₂SO₄) extract gave the crude product which was purified by f column chromatography over silica gel (20x4cm) using 10% EtOAc in hexanes as eluent to afford the pure ether 6 (1.39g, 81.28%yield) as a white solid. mp.65-66°C. ¹H-NMR (CDCl₃) δ 1.28-1.39 (m, 6H), 1.42 (s, 9H), 1.39-1.51 (m, 2H), 1.51-1.64 (m, 2H), 1.69-1.81 (m, 2H), 2.75-2.94 (m, 2H), 3.23-3.32 (m, 2H), 3.32-3.45 (m, 2H), 3.88 (t, 2H, J=6.52Hz), 4.88 (d, 1H, J=8.04Hz), 4.98 (s, 2H), 6.81 (d, 2H J=9.26Hz), 6.88 (d, 2H, J=9.21Hz) and 7.15-7.43 (m, 10H); ¹³CNMR (CDCl₃) δ 25.9, 26.1, 28.3 (2C), 29.29, 29.33, 29.5, 37.7, 51.5, 68.4, 70.3, 70.5, 71.1, 79.1, 115.2, 115.6, 126.1, 127.3, 127.7, 128.2, 128.4, 129.4, 137.2, 138.2, 152.7, 153.4 and 155.3; IR (neat):1685, 3373cm⁻¹; MS (ES⁺): 562 (M+1); Anal. Calcd for C₃₅H₄₇NO₅: C, 74.83; H, 8.43; N 2.49; found: C, 74.59; H, 8.39 and N, 2.56.

Compound 7

To a solution of Boc-protected ether 6 (1.00g, 1.782mmol) in CH₂Cl₂ (5mL) at room temperature a solution of TFA (5mL) in CH₂Cl₂ (5mL) was added and stirred at room temperature for 30min. TLC (10% MeOH in CHCl₃) showed that the reaction is complete. Solvent and TFA were removed completely under vacuum and residue was dissolved in CH₂Cl₂ (20mL). It was washed with sat. Na₂CO₃ (2x10mL), water (2x10mL) and brine (10mL). Removal of solvent from the dried (Na₂SO₄) extract gave the crude product. Purified by column chromatography over silica gel (15x3cm) using 10% MeOH in CHCl₃ to obtain the pure amine 7 (0.711g, 86.51% yield) as a colorless oil. ¹H-NMR (CDCl₃) δ 1.28-1.38 (m, 6H), 1.38-1.50 (m, 4H), 1.50-1.64 (m, 2H), 1.67-1.79 (m, 2H), 2.52 (dd, 1H, J₁=13.19Hz, J₂=7.29Hz), 2.76 (dd, 1H, J₁=13.34Hz, J₂=4.45Hz), 3.15-3.27 (m, 2H), 3.33-3.48 (m, 3H), 3.86 (t, 2H, J=6.44Hz), 4.96 (s, 2H), 6.80 (d, 2H, J=9.12Hz), 6.87 (d, 2H, J=8.92Hz) and 7.15-7.43 (m, 10H); ¹³CNMR (CDCl₃) δ 25.8, 25.9, 29.2 (2C), 29.3, 29.5, 40.6, 52.2, 68.3, 70.4, 71.1, 75.2, 115.1, 115.6, 126.1, 127.3, 127.7, 128.3, 128.4, 129.1,

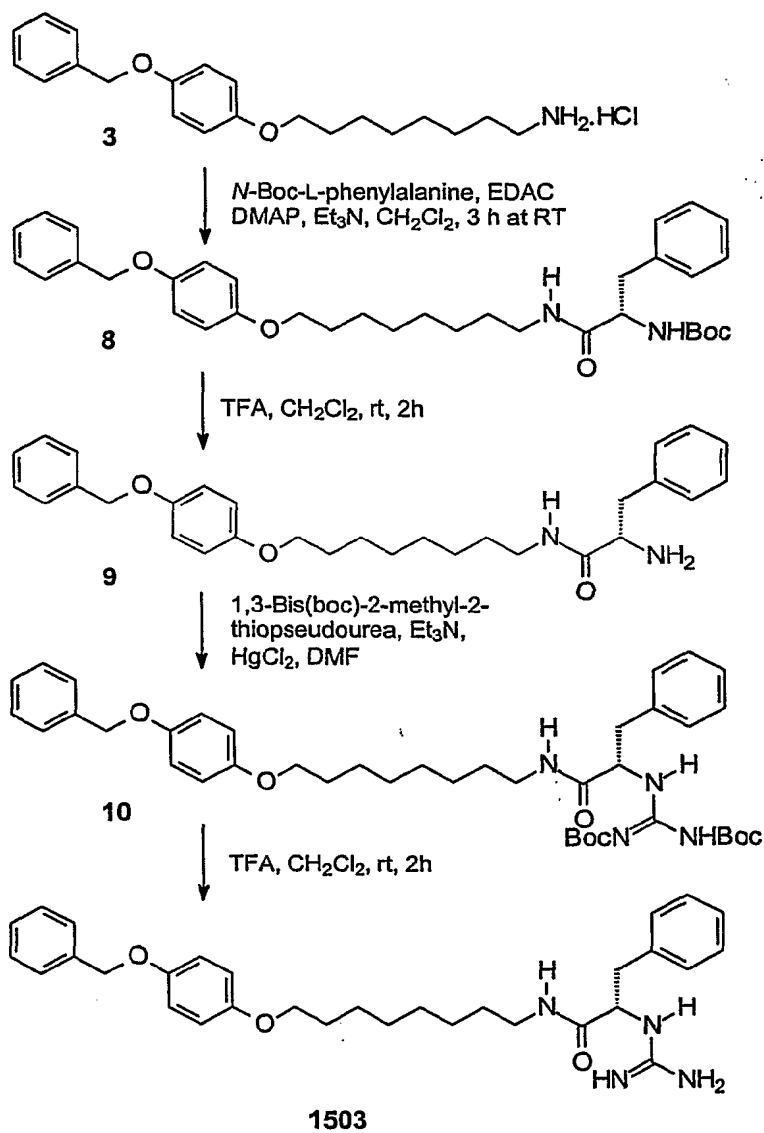
137.2, 138.8, 152.6 and 153.3; MS (ES⁺): 462 (M+1); Anal. Calcd for C₃₀H₃₉NO₃: C, 78.05; H, 8.52; N 3.03; found: C, 77.83; H, 8.56 and N, 3.02.

Compound 1439

5 To a solution of the amine **7** (0.7g, 1.518mmol) in DME (15mL) was added potassium carbonate (1.25g, 9.057mmol) and iodomethane (1.4mL, 22.4mmol). The reaction mixture was stirred at room temperature overnight. TLC (10% MeOH in CHCl₃) showed that the reaction is complete. Precipitation of the product was observed. CHCl₃ was added to the reaction mixture until all the product went into a solution. K₂CO₃ was
10 removed by filtration through celite 521. The filtrate was concentrated on a rotary evaporator until solid began precipitating out. This was filtered and washed with DME and ethyl acetate to obtain pure **1439** (0.518g, 54.08% yield) as a white solid., mp.128-129°C. ¹H-NMR (CDCl₃) δ 1.29-1.40 (m, 6H), 1.40-1.52 (m, 2H), 1.52-1.63 (m, 2H), 1.69-1.81 (m, 2H), 3.12 (t, 1H, J=12.26Hz), 3.22-3.43 (m, 4H), 3.58 (s, 9H), 3.84-3.95 (m, 3H), 4.25-
15 4.33 (m, 1H), 5.00 (s, 2H), 6.81 (d, 2H, J=9.15Hz), 6.90 (d, 2H, J=9.14Hz) and 7.21-7.45 (m, 10H); ¹³CNMR (CDCl₃) δ 25.9, 26.1, 29.18, 29.2, 29.24, 29.3, 31.3, 53.4, 65.1, 68.4, 70.5, 71.7, 73.8, 115.2, 115.6, 127.3, 127.5, 127.7, 128.4, 129.0, 129.4, 134.7, 137.1, 152.7 and 153.3; MS (ES⁺): 504 (M+); Anal. Calcd for C₃₃H₄₆INO₃: C, 62.75; H, 7.34; N 2.22; found: C, 62.40; H, 7.17 and N, 2.17.

Synthesis of guanidine 1503

Scheme 3



5

Compound 8

Compound 3 (free amine, 1.0 g, 3.05 mmol), *N*-Boc-L-phenylalanine (0.89 g, 3.35 mmol), 1-[3-[(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.72 g, 3.66

mmol), and DMAP (0.036 g, 0.30 mmol) was dissolved in 20 mL of anhydrous CH_2Cl_2 . The mixture was stirred at room temperature for 3 h, diluted with CHCl_3 (50 mL) and washed with 5% NaHCO_3 solution (2x30 mL) followed by brine (1x30 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The product was purified by flash silica gel column chromatography using hexanes/ CHCl_3 /MeOH (3/1/0.1) to afford **8** (1.5g, 86% yield) as a white solid. m.p.: 108-110°C.; ^1H NMR (CDCl_3) δ 1.17-1.45 (m, 10H), 1.41 (s, 9H), 1.69-1.82 (m, 2H), 2.96-3.18 (m, 4H), 3.89 (t, 2H, $J=6.5$ Hz), 4.26 (q, 1H, $J=7.6$ Hz), 5.01 (s, 2H), 5.09 (bs, 1H, -NH), 5.67 (bs, 1H, -NH), 6.82 (d, 2H, $J=9.2$ Hz), 6.90 (d, 2H, $J=9.2$ Hz), 7.19-7.41 (m, 10H); ^{13}C NMR (CDCl_3) δ 26.19, 26.87, 28.48, 29.35, 29.44, 29.53, 29.54, 38.98, 39.62, 68.69, 70.87, 115.55, 115.98, 127.67, 128.07, 128.74, 128.86, 129.52, 137.50, 153.03, 153.66, 171.11.; MS (ES+) 575 (M+1), 475 (M+1-Boc); (ES-) 573 (M-1).

Compound 9

To a solution of compound **8** (1.5 g, 2.61 mmol) in 10 mL of anhydrous CH_2Cl_2 was added 5 mL of trifluoroacetic acid in 5 mL of anhydrous CH_2Cl_2 at room temperature under argon atmosphere. The mixture was stirred for 30 min and the reaction was quenched by an addition of 10 g of solid NaHCO_3 . The mixture was partitioned between water (50 mL) and CHCl_3 (2x100 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The product was crystallized from ether to afford **9** (1.2g, 97% yield) as a white solid. m.p.: 82-84°C.; ^1H NMR (CDCl_3) δ 1.30-1.57 (m, 10H), 1.67-1.77 (m, 2H), 2.68 (dd, 1H, $J=9.1, 13.6$ Hz), 3.15-3.27 (m, 3H), 3.54 (dd, 1H, $J=4.3, 9.1$ Hz), 3.85 (t, 2H, $J=6.5$ Hz), 4.95 (s, 2H), 6.79 (d, 2H, $J=9.2$ Hz), 6.87 (d, 2H, $J=9.2$ Hz), 7.17-7.37 (m, 10H); ^{13}C NMR (CDCl_3) δ 25.93, 26.77, 29.15, 29.21, 29.28, 38.98, 41.01, 56.37, 68.40, 70.50, 115.26, 115.68, 126.66, 127.37, 127.77, 128.44, 128.57, 129.25, 137.25, 137.95, 152.74, 153.39, 174.00; MS (ES+) 475 (M+1).

Compound 10

To a stirred solution of compound **9** (0.1 g, 0.21 mmol) in DMF was added triethylamine (0.073 mL, 0.52 mmol) and HgCl_2 (0.095 g, 0.35 mmol). The mixture was cooled down to 0°C and bis-Boc-S-methyl-isothiourea (0.091, 0.31 mmol) was added at once. The mixture was stirred for 3 h and after the filtration of resulting white solid, the

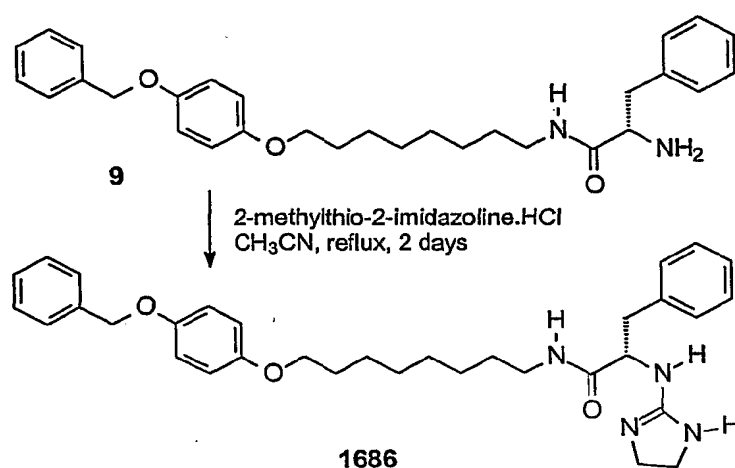
filtrate was partitioned between 5% NaHCO₃ (50 mL) and EtOAc (3x50 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The product was purified by silica gel column chromatography using hexanes/EtOAc (15/1 to 7/1) to afford **10** (0.14g, 93% yield) as a colorless oil; ¹H NMR (CDCl₃) δ 1.20-1.55 (m, 10H), 1.48 (s, 18H), 1.69-1.77 (m, 2H), 3.05-3.18 (m, 4H), 3.88 (t, 2H, *J* = 6.5 Hz), 4.67 (q, 1H, *J* = 7.2 Hz), 5.00 (s, 2H), 6.42 (1H, pseudo t, -NH), 6.82 (d, 2H, *J* = 9.3 Hz), 6.90 (d, 2H, *J* = 9.3 Hz), 7.18-7.44 (m, 10H), 8.81 (d, 1H, *J* = 7.2 Hz, -NH), 11.31 (s, 1H, -NH); ¹³C NMR (CDCl₃) δ 26.14, 26.28, 26.84, 28.13, 28.39, 29.30, 29.38, 29.48, 37.76, 39.55, 56.06, 68.60, 70.78, 79.45, 83.60, 115.47, 115.90, 126.99, 127.61, 128.00, 128.63, 128.67, 129.66, 137.02, 137.44, 152.79, 152.95, 153.59, 155.90, 163.14, 170.21; MS (ES+) 717 (M+1); (ES-) 715 (M-1).

Compound 1503

To a solution of compound **10** (0.3 g, 0.42 mmol) in 2 mL of anhydrous CH₂Cl₂ was added 1 mL of trifluoroacetic acid in 1 mL of anhydrous CH₂Cl₂ at room temperature under argon atmosphere. The mixture was stirred for 1 h and evaporated under reduced pressure. The residue was partitioned between 5% Na₂CO₃ (50 mL) and EtOAc (3x50 mL). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The product was purified by silica gel column chromatography using CHCl₃/MeOH/30% NH₄OH (10/1/0.1) to afford 0.17 g of free base of **1503** as a amorphous solid (79% yield). A solution of free base of **1503** (50 mg) in 3 mL of anhydrous CH₂Cl₂ was added 50 μL of trifluoroacetic acid and the mixture was evaporated with anhydrous ether (5x10mL). The resulting white crystal was suspended with ether and collected by filtration to give **1503** (0.045g, 74% yield). m.p.: 108-113°C; ¹H NMR (free base, CDCl₃) δ 1.11-1.55 (m, 10H), 1.68-1.77 (m, 2H), 2.85-3.23 (m, 4H), 3.86 (t, 2H, *J* = 6.5 Hz), 4.82 (bs, 1H), 4.97 (s, 2H), 6.80 (d, 2H, *J* = 9.2 Hz), 6.88 (d, 2H, *J* = 9.2 Hz), 7.21-7.41 (m, 10H), 7.95 (bs, 2H, -NH₂), 8.23 (bs, 1H, -NH); ¹³C NMR (CDCl₃) δ 26.17, 26.81, 28.73, 29.31, 29.38, 29.53, 40.13, 68.66, 70.80, 115.49, 115.94, 127.65, 128.02, 128.69, 128.96, 129.30, 135.04, 137.45, 152.98, 153.62, 157.09, 171.22; MS (ES+) 517 (M+1).

Synthesis of cyclic guanidine compound 1686 (Scheme 4)**Compound 1686**

A solution of compound **9** (0.05g, 0.105mmol) and 2-methylthio-2-imidazoline hydroiodide (0.14g 0.580mmol) in anhydrous CH₃CN was refluxed for 2 days. The mixture
 5 was cooled down and evaporated under reduced pressure. The residue was

Scheme 4

suspended with CH₂Cl₂ and any solid was removed by filtration. The filtrate was concentrated and purified by silica gel column chromatography using [NH₄OH saturated
 10 CHCl₃/MeOH (100/1 to 10/1) and crystallization from ether to give 30 mg of **1686** (0.03g, 53% yield) as a white solid. ¹H NMR (free base, CDCl₃, δ ppm) 1.18-1.52 (m, 10H), 1.65-1.79 (m, 2H), 2.74 (dd, 1H, *J* = 9.2, 13.1 Hz), 3.10-3.41 (m, 7H), 3.52 (bs, 1H, -NH), 3.89 (t, 2H, *J* = 6.5 Hz), 3.85-3.94 (m, 1H), 4.82 (bs, 1H), 5.01 (s, 2H), 6.78 (d, 2H, *J* = 9.2 Hz), 6.90 (d, 2H, *J* = 9.2 Hz), 7.22 (m, 1H, -NH), 7.26-7.41 (m, 10H); ¹³C NMR (CDCl₃, δ ppm)
 15 26.19, 27.03, 29.41, 29.47, 29.53, 29.59, 39.29, 40.85, 43.69, 62.06, 68.71, 70.85, 115.53, 115.96, 126.69, 127.68, 128.05, 128.69, 128.73, 129.64, 137.49, 139.37, 153.00, 153.64, 160.14, 173.33.; MS (ES⁺) 543 (M+1); (ES⁻) 541 (M-1).

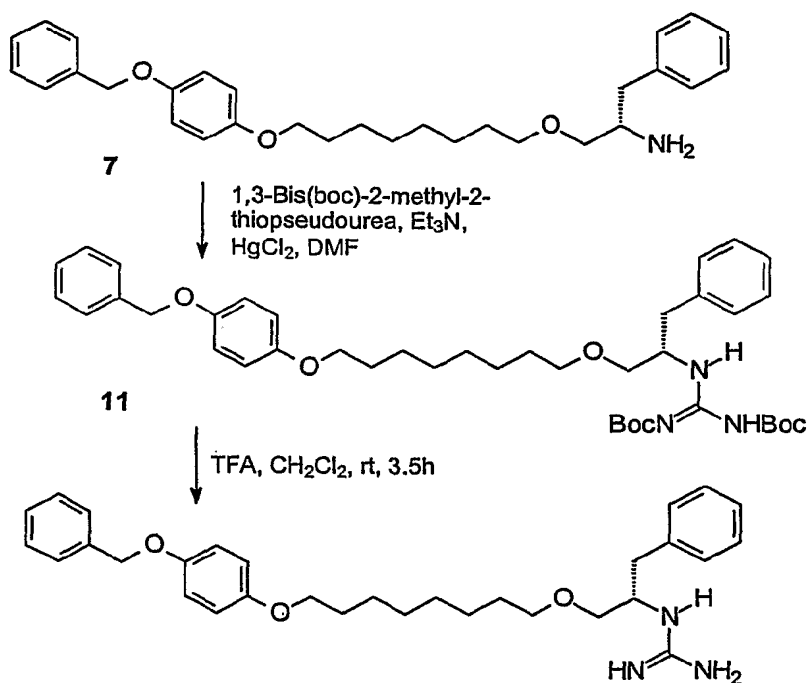
Synthesis of guanidine compound 1679 (scheme 5)**Compound 11**

To a solution of **7** (0.30g, 0.65mmol) in anhydrous DMF (4mL), Et₃N (0.35mL, 2.63mmol) and 1,3-bis (*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (0.208g, 0.717mmol) were added and stirred for 5 min at r.t. HgCl₂ (0.194g, 0.715mmol) was added to the reaction mixture and stirring continued at r.t. for 30 min. TLC (10% MeOH in CHCl₃) showed that the reaction is complete. Diluted with EtOAc (20mL) and the white solid formed was filtered off through celite 521. Filtrate was washed with water (3x5mL), brine (5mL) and dried (Na₂SO₄). Removal of solvent gave the crude product which was purified by column (15x2cm) chromatography over silica gel using 10% EtOAc in hexanes as eluent to afford the pure product **11** (0.218g, 92.8% yield); ¹H-NMR (CDCl₃) δ 1.27-1.43 (m, 8H), 1.47 (s, 9H), 1.50 (m, 9H), 1.53-1.65 (m, 2H), 1.67-1.81 (m, 2H), 2.83-3.02 (m, 2H), 3.25-3.35 (m, 2H), 3.39 (t, 2H, J=6.30Hz), 3.88 (t, 2H, J=6.53Hz), 4.41-4.54 (M, 1H), 4.98 (s, 2H), 6.81 (d, 2H, J=9.18Hz), 6.88 (d, 2H, J=9.21Hz), 7.15-7.43 (m, 10H), 8.66 (d, 1H, J=8.34Hz) and 11.48 (s, 1H); ¹³CNMR (CDCl₃) δ 25.9, 26.0, 27.9, 28.2, 29.2, 29.3, 29.4, 29.5, 37.2, 51.4, 68.3, 69.4, 70.4, 71.1, 78.7, 82.6, 115.2, 115.6, 126.2, 127.3, 127.7, 128.1, 128.4, 129.5, 137.2, 137.9, 152.6, 152.8, 153.3, 155.5 and 163.6; MS (ES⁺): 704 (M+1); Anal. Calcd for C₄₁H₅₇N₃O₇: C, 69.96; H, 8.16; N 5.97; found: C, 69.91; H, 8.10 and N, 5.93.

Compound 1679

To a solution of **11** (0.16g, 0.227mmol) in CH₂Cl₂ (2mL) a solution of TFA (2mL) in CH₂Cl₂ (2mL) was added and stirred at r.t. for 3.5h. TLC (in 10% MeOH in CHCl₃) showed that the reaction is complete. Solvent and TFA were completely removed, redissolved in CH₂Cl₂ (20mL), washed with sat. Na₂CO₃ (3x5mL), water (2x5mL) and brine (5mL). Removal of solvent from the dried (Na₂SO₄) extract gave the crude product which was purified by column (10x2cm) chromatography over silica gel using 10% MeOH in CHCl₃ as eluent to afford the pure guanidine derivative **1679** (0.082g, 71.65% yield); ¹H-NMR (CDCl₃) δ 1.17-1.45 (m, 8H), 1.45-1.61 (m, 2H), 1.65-1.81 (m, 2H), 2.73-2.87 (m, 1H), 2.87-3.04 (m, 1H), 3.25-3.43 (m, 3H), 3.43-3.56 (m, 1H), 3.65-3.80 (m, 1H), 3.86 (t,

2H, J=6.46Hz), 4.96 (s, 2H), 6.80 (d, 2H, J=9.18Hz), 6.88 (d, 2H, J=8.97Hz), 7.03 (bs, 1H), 7.16-7.49 (m, 12H, Ar-H and NH₂) and 8.09 (d, 1H, 6.54Hz); ¹³CNMR (CDCl₃) δ 25.6, 25.7, 29.0 (2C), 29.1(2C), 37.1, 55.1, 68.2, 70.4, 71.6, 73.9, 115.1, 115.5, 126.8, 127.2, 127.6, 128.3, 128.5, 128.8, 136.4, 137.1, 152.5, 153.2 and 158.8; IR (neat): 3155, 3259, 3329 cm⁻¹; MS (ES⁺): 504 (M+1); Anal. Calcd for C₃₃H₄₂F₃N₃O₅ (TFA salt): C, 64.17; H, 6.85; N 6.80; found: C, 64.68; H, 7.06 and N, 6.78.

Scheme 5

EXAMPLE 2

5 This example illustrates some of the properties of compounds of the present invention.

Antimicrobial Testing (*P. aeruginosa*, *E. coli*, *B. subtilis*, *S. aureus*, *S. aureus* (MCR), *A. niger* and *M. flavescens*.)

10 The MIC test procedures conformed to the present protocol from the National Committee for Clinical Laboratory Standards (NCCLS), and were designed to provide basic antimicrobial data on compounds based on the MIC of the active component.

The test compounds were solubilized, diluted, and pipetted in duplicate into 10 mL sterile culture tubes and dried under vacuum.

15 Challenge organisms, specified were grown overnight at 37°C in the appropriate medium (i.e., Mueller-Hinton Broth). These pure broth cultures were diluted 1:1,000 and 2.0 mL were added to the test compound tubes.

Appropriate media controls, challenge organism viability controls, and antibiotic control dilutions (i.e., ampicillin and nystatin), were prepared in the same manner as the test compounds and run against the challenge organisms.

20 The cultures were incubated overnight at 37°C and MIC's in µg/mL were indicated by visual determination of the first clear tube.

The minimum inhibitory concentration (MIC) was defined as the concentration of test compound that completely inhibited growth of the challenge organism.

25 **Antimicrobial Testing (*B. anthracis*).**

To determine the MIC of each compound in liquid bacterial culture medium against spores of *Bacillus anthracis* Sterne 34F2, an MIC range of 128µg/mL – 0.0156µg/mL was tested in triplicate using a 48-well, tissue culture plate. Dilutions (of up to 1:7.8) of each compound (stock concentration 1.0mg/mL in 100% methanol) were made in 2X M-H broth. Spores were suspended to 1X10⁶ spores/400µl in filter-sterilized MilliQ water.

**Potency of Various Compounds to Inhibit Gram- Negative Bacterial Growth or the
Growth of Two Fungi *In Vitro***

Compound No.	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. niger</i>
1197	> 50	> 50	< 1.56	< 6.25
1364	> 50; > 50	< 50; > 50	< 1.56; < 12.56	> 50; > 50
1420	> 50	> 50	< 3.13	> 50
1423	> 50	> 50	< 3.13	< 50
1439	> 50	< 12.5	< 3.13	< 25
1447	> 50; > 50	> 50; < 50	< 6.25; < 3.13	> 50; > 50
1450	> 50	> 50	< 6.25	> 50
1503	> 50	> 50	> 50	> 50
Ciprofloxacin	< 5.0	< 5.0	-	-
Doxycycline	< 30	< 1.56	-	-
Amphotericin B	-	-	< 1.56	< 1.56

5 All values are reported as µg/mL.

Potency of Various Compounds to Inhibit Bacterial Growth *In Vitro*

Compound No.	<i>B.subtilis</i>	<i>S. aureus</i>	<i>S. aureus</i> (MCR)	<i>B. anthracis</i>	<i>M. flavescens</i>
1197	< 0.78	< 0.78	< 0.78	-	-
1364	< 0.39; < 6.25	< 0.78; < 2.5	< 0.78; < 1.56	-	> 50
1391	< 3.13	-	< 1.56	-	-
1420	< 0.39	< 1.56	< 0.78	-	-
1423	< 0.20	< 1.56	< 1.56	-	-
1439	< 0.39	< 0.78	< 1.56	4; 4	< 12.5
1447	< 1.56 < 0.78	< 1.56; < 0.78	< 1.56; < 1.56	-	< 6.25
1450	< 3.13	< 3.13	< 3.13	-	< 3.13
1484	< 3.13		< 0.78	-	
1503	< 0.78; < 3.13	< 0.78	< 0.78; < 1.56	8; 16	> 50
1505	< 0.78	-	< 0.78	-	-
1594	> 50	-	< 6.25	8; 32	-
1617	< 12.5	-	< 6.25	16; -	-
1685	< 3.13	-	< 0.78	4; 4	-
Ciprofloxacin	< 5.0; < 0.5	< 5.0	< 5.0; < 0.5	0.25; 0.125	
Doxycycline	< 1.56	< 1.56	< 30	-	
Ampicillin	< 0.5; < 0.2		> 50	-	

- 5 Values are reported as $\mu\text{g/mL}$ and represent the Minimal Inhibitory Concentration (MIC) for each assay.

Where multiple values are shown (*B.subtilis*, *S. aureus*, *S. aureus* (MCR)), these represent two or more tests performed.

- For assays using *B. anthracis*, the approximate MICs were determined for various compounds in a standard broth dilution assay using bacterial growth media or by visually inspecting the samples for turbidity (appearance of bacterial outgrowth) when bacteria were cultured in mammalian cell culture media.
- 10

Cytotoxicity in Murine 3T3 Cells.**Methods**

Prior to conducting the assay, cell number, serum concentration, and medium conditions were optimized. Then using the assay conditions as described below, cells were seeded on day 1 and allowed to adhere for at least 1 hour. Test articles were added to achieve a final concentration of 10, 50 and 100 μ M in the cultures (Note: in an initial assay, a concentration of 500 μ M was included but due to solubility issues as well as marked cytotoxicity, this concentration was excluded from the final assay). The initial solubilization of the test articles was in 50:50 methanol:water (v/v). (Note: Compound 1364 went into solution on day 1, but precipitated on day 2. The organic solvent was increased from 50% to 66%.(v/v)). Compound 1439 never went into solution at 50% organic. Compound 1503b went into solution at 50% organic. Maximum concentration of methanol did not exceed 1.6% in the final assay. On day 1, compounds 1439 and 1364 required sonication before solubility was reached). The cells plus compound were incubated overnight at 37°C, under a 5% CO₂/95% O₂ atmosphere. On day 2, the cells in the positive control wells were lysed with 0.9% Triton X-100 for 45 minutes to establish maximum levels of LDH release. The plates were centrifuged at 250 x g for 5 minutes, the supernatants transferred to a new assay plate, and the LDH was measured. The assay plates were read at OD 490 nm.

Experimental Conditions**Assay Conditions**

<i>Culture Medium</i>	DMEM, 10% calf serum
<i>Control: Maximum LDH release</i>	Lysis with Triton X-100 at 0.9%
<i>Control: Spontaneous LDH release</i>	Cells with no compound added
<i>Control: LDH standard</i>	Bovine heart LDH (included in kit)
<i>Incubation Conditions</i>	37°C for 20 hrs; 5% CO ₂ /95% O ₂
<i>Compound Concentrations</i>	10 μ M, 50 μ M, 100 μ M
<i>Enzyme Assay</i>	Promega Cytotox 96 Cytotoxicity Assay

Abbreviations: DMEM Dulbecco's Modified Eagle's Medium

Cytotoxicity in Rabbit Primary Renal Cells.

Isolation of Proximal Tubules and Culture Conditions. Rabbit renal proximal tubules were isolated using the iron oxide perfusion method and grown in 35-mm tissue culture dishes under improved conditions. The cell culture medium was a 1:1 mixture of DMEM/Ham's F-12 (without D-glucose, phenol red, or sodium pyruvate) supplemented with 15 mM HEPES buffer, 2.5 mM L-glutamine, 1 μ M pyridoxine HCL, 15 mM sodium bicarbonate, and 6 mM lactate. Hydrocortisone (50 nM), selenium (5 ng/mL), human transferrin (5 μ g/mL), bovine insulin (10 nM) and L-ascorbic acid-2-phosphate (50 μ M) were added to fresh culture medium immediately prior to daily media change.

Treatment of RPRC. All numbered compounds were diluted in methanol and the final concentration of methanol in RPRC was less than 0.1% (v/v). 4-BOP also was dissolved in methanol while TMAI was dissolved in ethanol and ciprofloxacin was dissolved in media. These concentrations of solvents did not cause any increases in RPRC death alone.

Measurement of RPRC Death. Cell death was monitored in RPRC by assessment of both annexin V and PI staining using flow cytometry. Briefly, RPRC were exposed to the indicated concentrations of compounds for 24 hr. Media was removed and RPRC washed twice with phosphate-buffered saline (PBS) and incubated in a binding buffer (10 mM HEPES, 140 mM NaCl, 5 mM KCL, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, pH = 7.4) containing annexin V-FITC (1 μ mol) and PI (25 μ g/mL). After a 10 min incubation, RPRC were washed three times in the binding buffer and were released from the monolayers by gentle scrapping with a rubber policeman. Annexin V and PI staining were measured using a BectonDickson FacsCalibur flow cytometer (San Jose, CA). An equal number of cells (10,000) were counted for sample and apoptotic cells were defined as those that stained positive for annexin V-FITC only. RPRC undergoing necrotic cell death stained for PI only. Late apoptotic cells (RPRC dying initially by apoptosis and/or necrotic cell death that exhibited more extensive degradation of the plasma membrane over time) were defined as those that stained positive for both annexin V and PI.

Data Analysis. RPRC isolated from one rabbit represented one experiment (n=1). Data were analyzed and are reported as means \pm standard error of the mean of at least 3 separate experiments.

Effect of Various Compounds on Mammalian Cell Growth *In Vitro*

Compound No.	%CELLULAR NECROSIS (FIBROBLASTS) ¹	%CELLULAR NECROSIS (RPRC) ²	% APOPTOSIS (RPRC) ³
Control		2 ± 1	7 ± 1
TMAI	-	2 ± 1	5 ± 1
Cipro	-	4 ± 1	9 ± 3
1617	-	18 ± 2	23 ± 3
1594	-	29 ± 4	13 ± 2
1439	73	62 ± 2	10 ± 1
1364	62	63 ± 2	15 ± 3

5 1 – at 100 µM

2 – at 300 µM

3 – at peak effect (30 µM)

RPRC – rabbit primary renal cells

TMAI – tetramethylammonium iodide

10 Reference value 1 µM = approximately 0.6 to 0.7 µg/mL for compounds 1364, 1439, 1594 and 1617 contingent upon the molecular weight of the compound.

EXAMPLE 3

This Example illustrates the NAD synthetase enzyme inhibiting activity of some compounds of the present invention.

Prokaryotic NAD Synthetase Enzyme Activity Assay



The coupled assay – production of NAD was monitored through conversion to NADH by alcohol dehydrogenase. [NADH] was monitored by 2 parallel methods: the change in absorbance at 340 nm, and fluorescence at 460 nm (excitation 320 nm). The assay conditions were as follows: Total volume = 200 μL ; 58.5 mM HEPPS, pH 8.5; 18.5 mM NH_4Cl ; 9.75 mM MgCl_2 ; 1 % (v/v) EtOH; 0.3 % BOG (w/v); 40 $\mu\text{g/mL}$ ADH; 0.1 mM NaAD; 0.2 mM ATP; 2.0 $\mu\text{g/mL}$ NAD synthetase; 2.5 % (v/v) DMSO. Controls were included for determining inhibitor background, precipitation, and ADH inhibition.

Compound No.	IC_{50} (μM)			
	Mean	SD	SEM	N
1126	36.2			1
1127	23.0	1.8	0.37	23
1168	36.2			1
1169	36.2			1
1182	42.1	3.2	1.84	3
1186	46.1			2
1197	20.8	2.7	0.57	23
1264	38.1			2
1290	36.2			1
1291	36.2			1
1292	36.2			1
1294	36.2			1
1321	22.0	1.8	1.27	2
1322	26.5	4.8	3.41	2
1323	48.2			1
1324	50.7			1
1336	19.4	1.1	0.57	4
1337	20.3	2.0	0.99	4
1338	23.0	2.6	1.28	4
1339	19.8	1.7	0.85	4

Compound No.	IC ₅₀ (μM)			
	Mean	SD	SEM	N
1340	19.3	1.6	0.79	4
1358	46.6		0.00	2
1359	42.2	6.6	3.80	3
1364	48.4	14.7	4.90	9
1369	29.2	3.0	1.71	3
1370	16.9	0.9	0.45	4
1371	19.1	1.2	0.67	3
1387	20.5	5.8	2.58	5
1388	14.5	4.0	2.32	3
1389	45.5	8.5	4.93	3
1390	14.2	3.1	0.85	13
1391	11.5	2.9	0.60	24
1393	36.7	4.9	2.81	3
1394	22.5	4.0	2.32	3
1396	15.1	2.8	1.25	5
1397	16.9	3.0	1.76	3
1398	16.0	2.2	1.29	3
1401	>100μM			
1405	18.8			2
1408	30.5	5.3	3.03	3
1420	31.3	9.6	5.54	3
1421	34.8	2.8	1.98	2
1422	27.9	3.9	2.73	2
1423	32.9	12.8	7.36	3
1431	18.2	1.9	1.09	3
1432	16.6	3.3	0.99	11
1439	22.7	5.1	1.81	8
1442	21.4	1.9	1.38	2
1443	27.9	17.0	9.80	3
1447	22.1	6.2	2.06	9
1448	30.7	0.5	0.32	2
1450	31.7	9.0	4.03	5
1451	34.2	0.6	0.43	2
1454	23.9	2.7	1.90	2
1456	17.0	2.3	0.67	12
1475	22.6			1
1477	14.0	2.9	0.93	10
1478	15.8	10.5	3.17	11
1479	18.6	0.6	0.42	2
1482	26.2	8.3	5.88	2
1483	16.0	1.7	0.85	4
1484	14.8	6.3	1.89	11
1485	34.8			1
1486	37.8			1

Compound No.	IC ₅₀ (μM)			
	Mean	SD	SEM	N
1491	19.9	5.6	1.68	11
1494	12.5	5.6	1.68	11
1495	33.4	19.1	7.21	7
1498	39.4			1
1499	26.8			1
1501	38.2			1
1502	35.6			1
1503	12.7	3.4	0.72	23
1505	6.6	1.5	0.41	14
1593	18.1	3.3	2.33	2
1594	25.0	6.8	4.77	2
1596	28.0			1
1597	21.3			1
1599	44.0			1
1600	28.7	8.6	2.73	10
1603	34.9	12.2	3.39	13
1604	21.1	4.1	2.92	2
1605	21.0			1
1606	39.1			1
1608	26.3			1
1609	20.7			1
1610	30.4			1
1611	23.3	8.0	5.68	2
1612	26.2	12.0	8.48	2
1613	19.1	3.0	2.12	2
1614	23.1			1
1615	22.3	7.1	5.05	2
1616	38.5			1
1617	31.4	14.8	8.55	3
1619	22.3			2
1620	21.9			2
1621	25.5	14.8	14.81	1
1622	34.2			1
1623	33.9			1
1624	31.2			1
1629	21.1			1
1632	18.5			1
1633	20.4			1
1634	21.2			1
1635	35.1			1
1636	19.0	2.5	1.75	2
1637	23.3			1
1644	23.9			1
1645	18.1	5.4	3.80	2

Compound No.	IC ₅₀ (μ M)			
	Mean	SD	SEM	N
1650	>50 μ M			
1651	47.7			
1652	17.9			
1653	19.5			
1658	16.8	2.4	1.72	2
1661	23.7	7.8	3.20	6
1662	23.2	5.5	1.95	8
1663	18.4			1
1664	19.9			1
1665	19.6	2.5	0.79	10
1666	27.7			1
1678	36.5			1
1679	10.4	2.2	0.75	9
1680	10.1	1.2	0.37	11
1681	12.9	1.4	0.46	9
1682	17.6	3.7	1.38	7
1683	20.2			1
1685	9.9	1.7	0.60	8

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

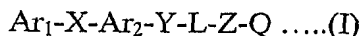
The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred

embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and
5 equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



wherein Q is Q_1Ar_3 or Ar_3Q_1 ;

5 Ar_1 , Ar_2 , and Ar_3 are independently aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ alkoxy $\text{C}_1\text{-C}_6$ alkyl, halo, amino, $\text{C}_1\text{-C}_6$ alkylamino, $\text{C}_1\text{-C}_6$ dialkylamino, $\text{C}_1\text{-C}_6$ trialkylamino, $\text{C}_1\text{-C}_6$ alkylamino $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ dialkylamino $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ trialkylamino $\text{C}_1\text{-C}_6$ alkyl, azido, amine oxide, hydroxy, 10 carboxyl, $\text{C}_1\text{-C}_6$ alkylcarbonyl, $\text{C}_1\text{-C}_6$ alkylcarbonyl $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkylcarbonyloxy, $\text{C}_1\text{-C}_6$ alkylcarbonyloxy $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkylloxycarbonyl $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkylloxycarbonyl, $\text{C}_1\text{-C}_6$ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, $\text{C}_1\text{-C}_6$ dialkyl sulfonamido, $\text{C}_1\text{-C}_6$ alkylcarbonylamino, formyl, formylamino, mercaptanyl, and heterocyclyl; optionally, a ring nitrogen atom of heteroaryl Ar_1 , Ar_2 , or Ar_3 may be 15 quaternized;

X, Y, and Z are independently selected from the group consisting of a covalent bond, $(\text{CH}_2)_m\text{O}$, $\text{O}(\text{CH}_2)_m$, $(\text{CH}_2\text{O})_m$, $(\text{OCH}_2)_m$, $(\text{CH}_2\text{CH}_2\text{O})_m$, $(\text{OCH}_2\text{CH}_2)_m$, $\text{C}(=\text{O})\text{O}$, $\text{OC}(=\text{O})$, $\text{OC}(=\text{O})\text{O}$, $(\text{CH}_2)_m\text{S}$, $\text{S}(\text{CH}_2)_m$, $(\text{CH}_2\text{S})_m$, $(\text{SCH}_2)_m$, NH , NR , $^+\text{NR}_2$, $\text{C}(=\text{O})\text{NH}$, $\text{C}(=\text{O})\text{NR}$, $\text{NHC}(=\text{O})$, $\text{NRC}(=\text{O})$, $\text{CH}(\text{OH})$, and $\text{CH}(\text{OR})$, wherein R is $\text{C}_1\text{-C}_6$ alkyl and m is 20 0-5;

L is $\{(\text{CR}_1\text{R}_2)_q\text{-(W)}_t\text{-(CR}_3\text{R}_4)_r\}_p$, wherein $\text{R}_1\text{-R}_4$ are independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ alkoxy $\text{C}_1\text{-C}_6$ alkyl, halo, amino, $\text{C}_1\text{-C}_6$ alkylamino, $\text{C}_1\text{-C}_6$ dialkylamino, azido, hydroxy, aldehyde, $\text{C}_1\text{-C}_6$ acetal, $\text{C}_1\text{-C}_6$ ketal, $\text{C}_1\text{-C}_6$ alkylcarbonyl, $\text{C}_1\text{-C}_6$ alkylcarbonyl $\text{C}_1\text{-C}_6$ alkyl, 25 $\text{C}_1\text{-C}_6$ alkylcarbonyloxy, $\text{C}_1\text{-C}_6$ alkylcarbonyloxy $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkylthio, nitro, nitrosyl, cyano, sulfonamido, $\text{C}_1\text{-C}_6$ alkylcarbonylamino, and heterocyclyl; W is a moiety selected from the group consisting of alicyclic ring, aromatic ring, heterocyclic ring, combinations of alicyclic, heterocyclic, and/or aromatic rings, $\text{C}_2\text{-C}_6$ alkenyl, dienyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_2\text{-C}_6$ alkenyloxy, $\text{C}_2\text{-C}_6$ alkynyloxy, anhydrido, enol, ketene, 30 amino, imino, hydrazinyl, epoxy, episulfide, amido, amine oxide, urea, urethane, ester, thioester, carbonate, carbonyl, thiocarbonyl, sulfonyl, diazo, sulfonamido, ether oxygen, ether sulfur, thionyl, silyl, peroxide, lactam, lactone, phenylene, monosaccharide, di-, tri-,

and higher polysaccharides, nucleic acid, amino acid, phosphonyl, phosphoryl, and combinations thereof; q, r, and t are independently 0-20; q, r, and t are not simultaneously 0; and p is 1-6; L, optionally, further including O, N, or S; and

Q₁ is (i) a C₁-C₆ alkylene, C₁-C₆ alkylene carbonyloxy C₁-C₆ alkyl, or C₁-C₆ alkylene carbonylamino C₁-C₆ alkyl group, optionally having one or more substituents selected from the group consisting of amino, C₁-C₆ alkylamino, C₁-C₆ haloalkylamino, C₁-C₆ haloalkyl C₁-C₆ alkyl amino, C₁-C₆ hydroxyalkylamino, C₁-C₆ hydroxyalkyl C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, and heterocyclic containing a nitrogen atom which may be optionally quaternized, (ii) a C₂-C₆ alkylene; (iii) methylene with the proviso that Z is other than covalent bond or O(C=O) when Q is Q₁Ar₃ wherein Ar₃ is a phenyl *para* substituted with amino, methylamino, dimethylamino, or trimethylamino or Ar₃ is a pyridyl or N-methyl pyridyl; (iv) a covalent bond with the proviso that when Ar₃ is pyridyl, N-methyl pyridyl, or phenyl *para* substituted with trimethylaminomethyl group, Z is other than a covalent bond or O(C=O); (v) a group containing amidine or guanidine function wherein the amidine or guanidine may be optionally N-substituted with a C₁-C₆ alkyl; or (vi) a zwitterion;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein Ar₁, Ar₂, and Ar₃ are independently aryl including 1-3 aromatic rings.

3. The compound of claim 1 or 2, wherein Ar₁, Ar₂, and Ar₃ are independently phenyl or substituted phenyl.

4. The compound of any of claims 1-3, wherein Ar₁, Ar₂, and Ar₃ are independently heteroaryl including 1-3 rings one or more of which include O, N, or S.

5. The compound of any of claims 1-3, wherein Ar₁ is phenyl or phenyl substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy,

carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and
5 heterocyclyl.

6. The compound of claim 5, wherein Ar₁ is phenyl or phenyl substituted with one or more substituents selected from the group consisting of C₁-C₆ alkoxy, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, azido, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylthio, nitro, cyano, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, and
10 heterocyclyl.

7. The compound of any of claims 1-3, wherein Ar₂ is phenyl, optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and
15
20 heterocyclyl.

8. The compound of any of claims 1-3, wherein Ar₂ is indolyl or indolyl substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-
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C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and heterocyclyl.

9. The compound of claim 1, wherein Ar₃ is phenyl, indolyl, or pyridyl, optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl, C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and heterocyclyl.
10. The compound of claim 1 or 9, wherein Ar₃ is phenyl, optionally substituted with one or more substituents selected from the group consisting of C₁-C₆ alkoxy and C₁-C₆ trialkylamino.
11. The compound of claim 9, wherein Ar₃ is indolyl.
12. The compound of claim 11, wherein Q is Ar₃Q₁.
13. The compound of claim 12, wherein Q₁ is C₁-C₆ alkylenyl carbonyloxy C₁-C₆ alkyl, optionally having a C₁-C₆ trialkylamino
14. The compound of claim 12, wherein Q₁ is trimethylamino ethylenyl carbonyloxy t-butyl.
15. The compound of claim 12, wherein Q₁ is C₁-C₆ alkylenyl, optionally having a C₁-C₆ trialkylamino or a heterocyclic containing a quaternized nitrogen atom.
16. The compound of claim 12, wherein Q₁ is a covalent bond.

17. The compound of claim 12, wherein Q₁ is a zwitterion.

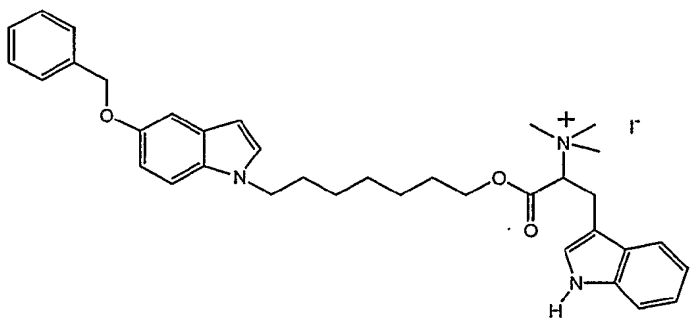
18. The compound of claim 12, wherein Q₁ is a group containing amidine or guanidine
5 function wherein the amidine or guanidine may be optionally N-substituted with a C₁-C₆ alkyl.

19. The compound of any of claims 18, wherein t is 0.

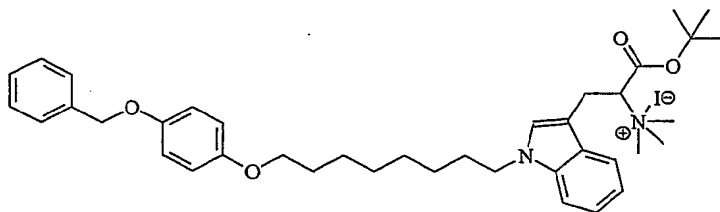
10 20. The compound of claim 19, wherein R₁-R₄ are H.

21. The compound of claim 20, wherein q and r are independently 1-7.

15 22. The compound of any of claims 1-21, wherein said compound is selected from the group consisting of:

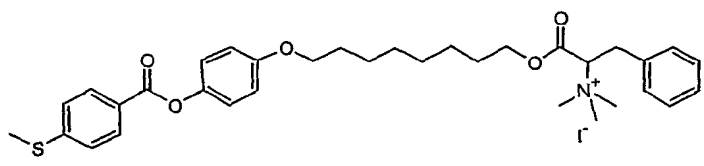


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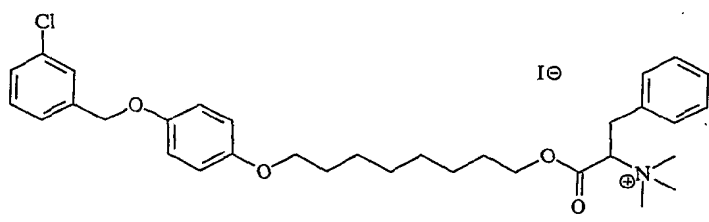


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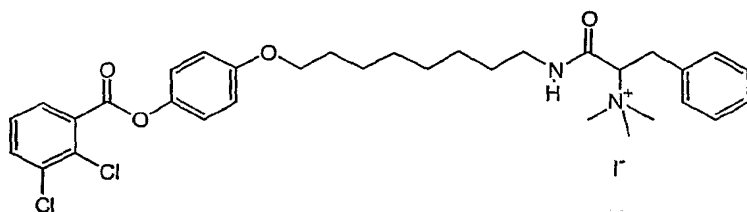
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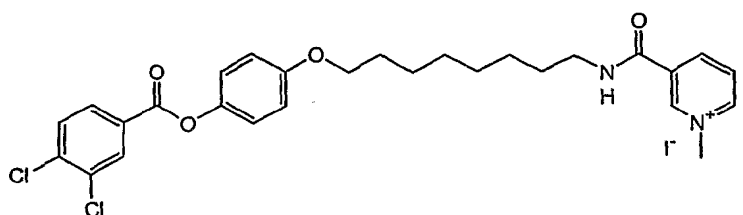
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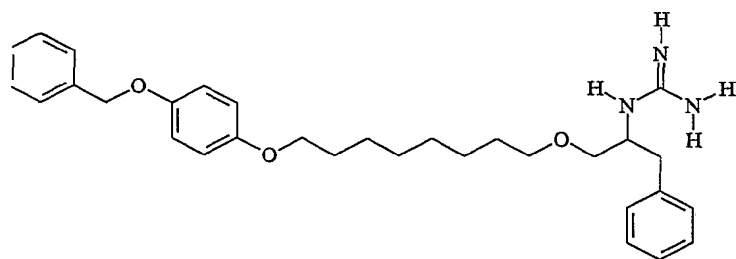
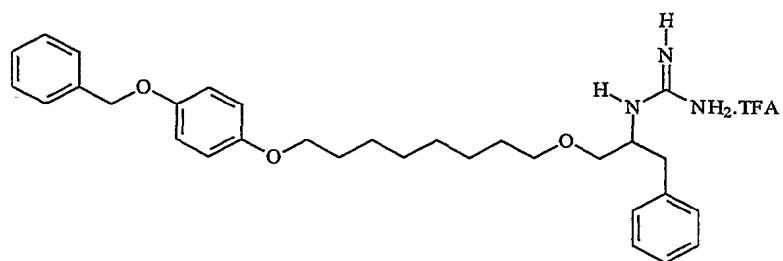
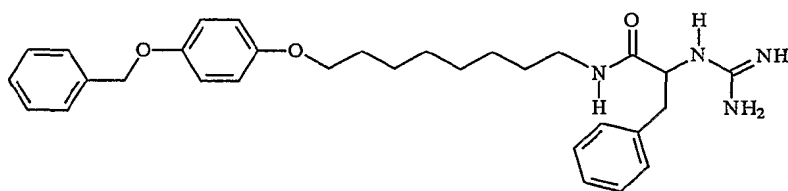
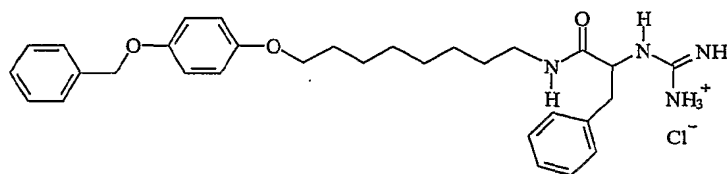


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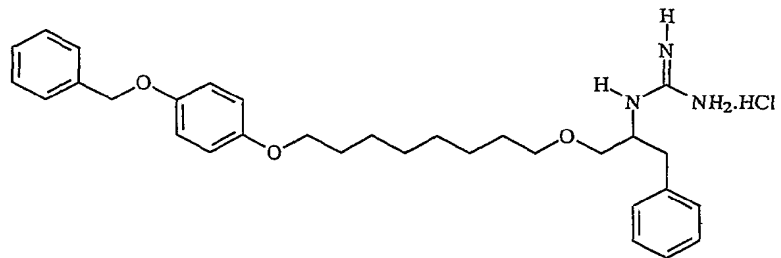


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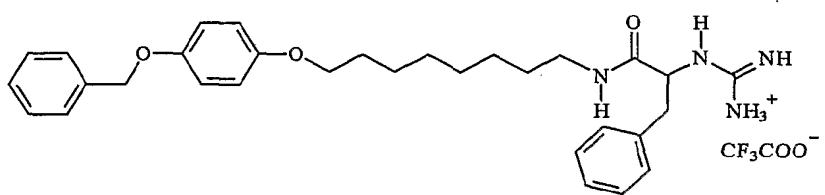
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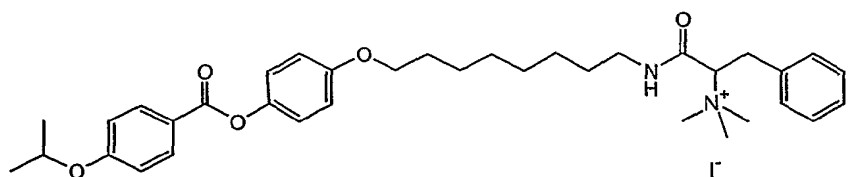


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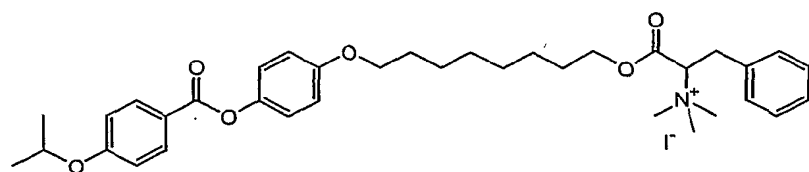


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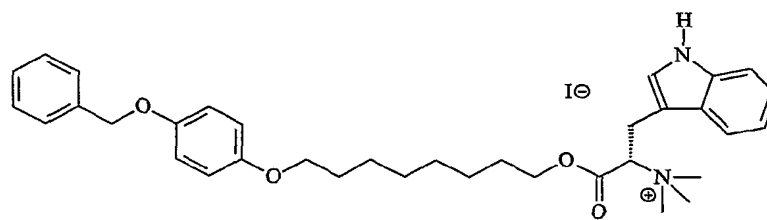


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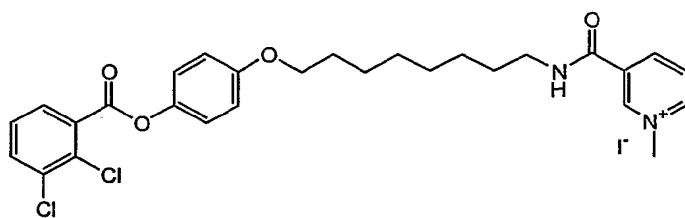
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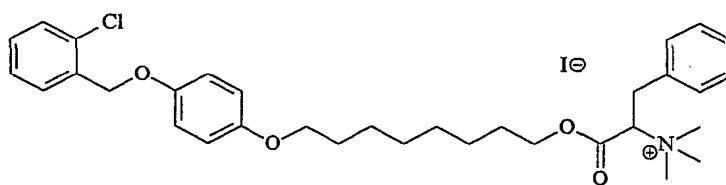
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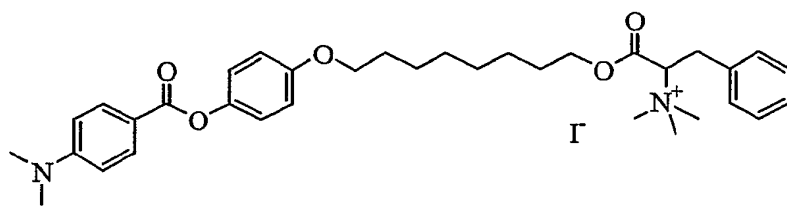


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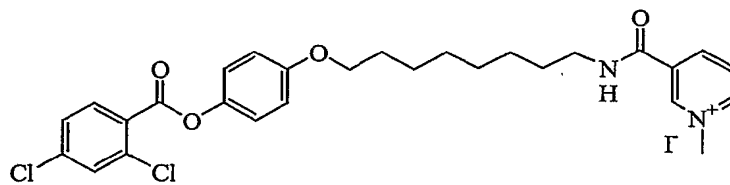


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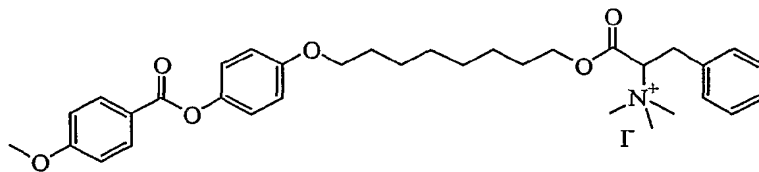
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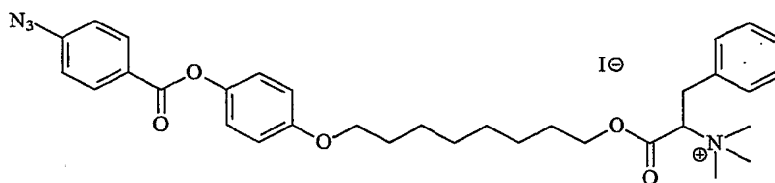
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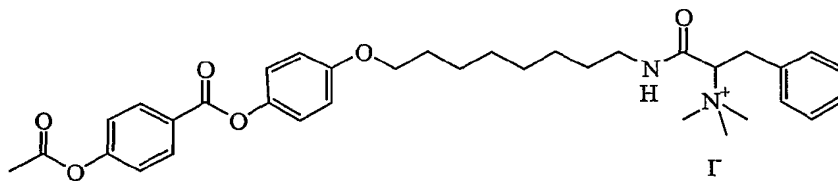
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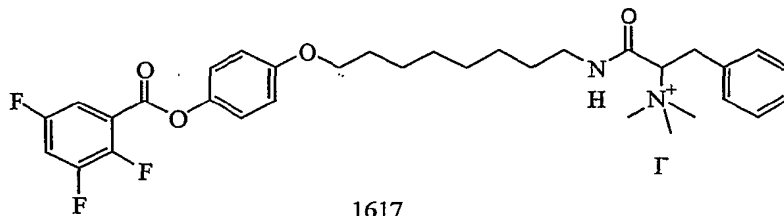
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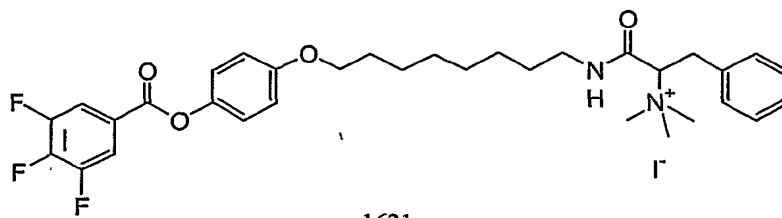
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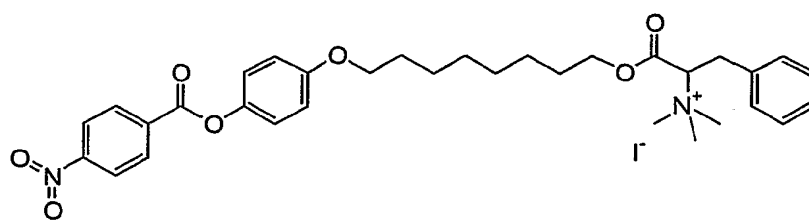
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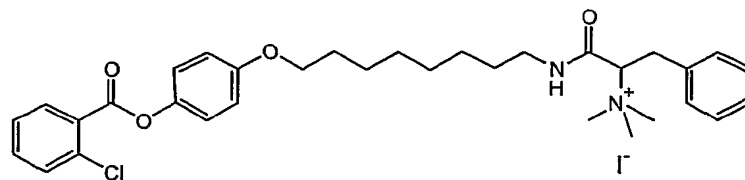
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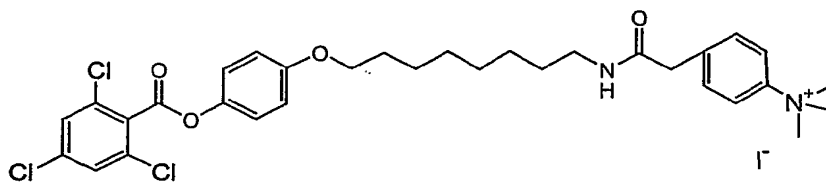
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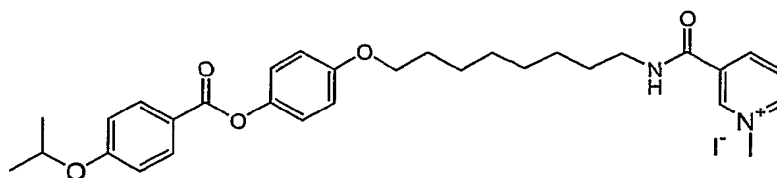


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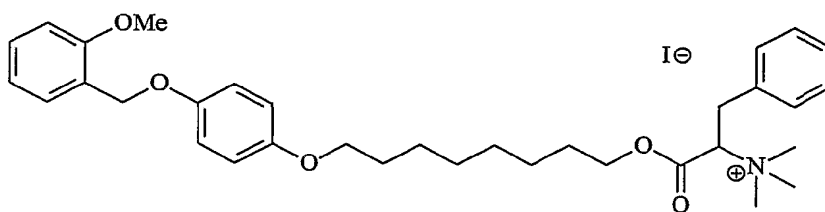
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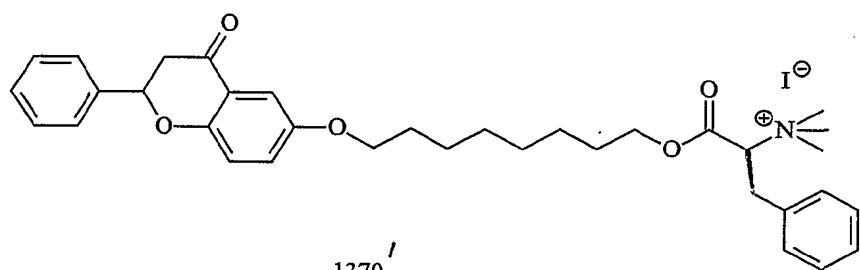
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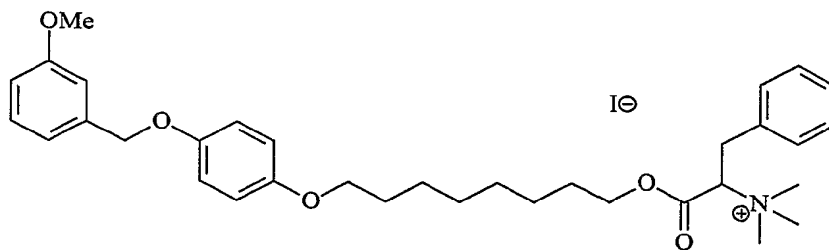
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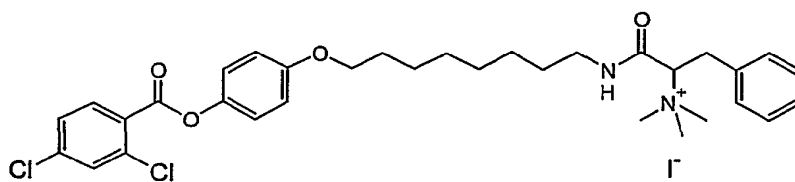
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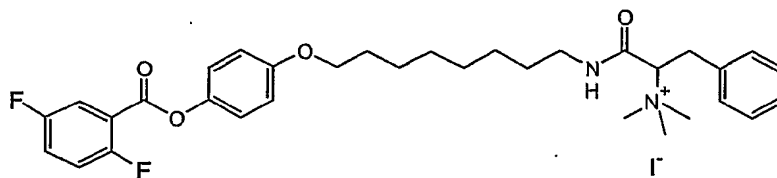
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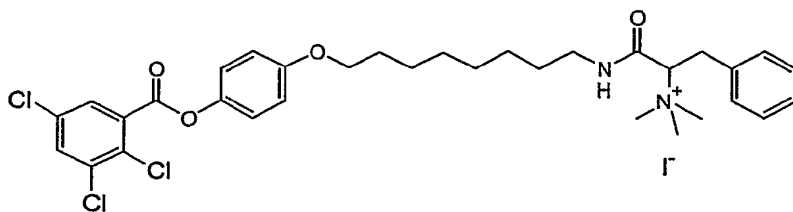


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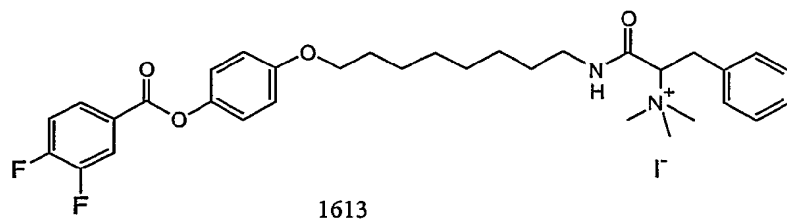


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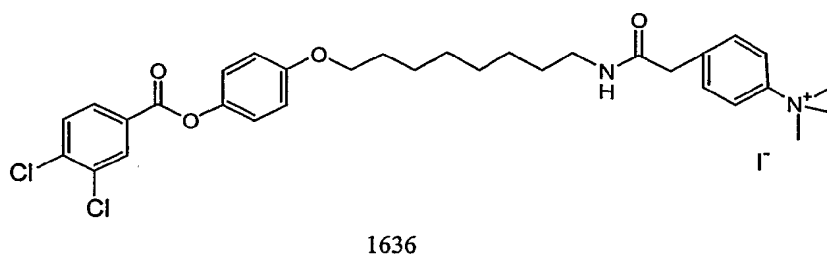


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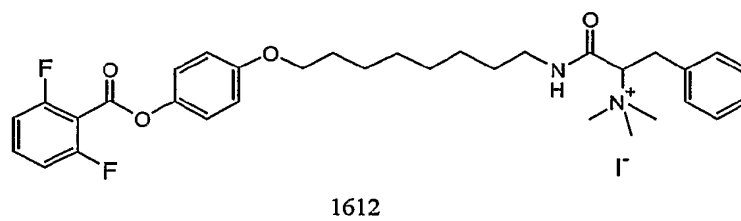
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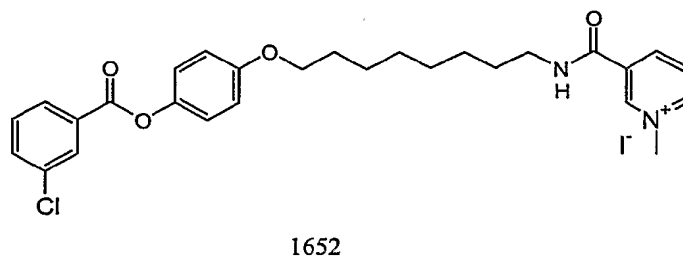
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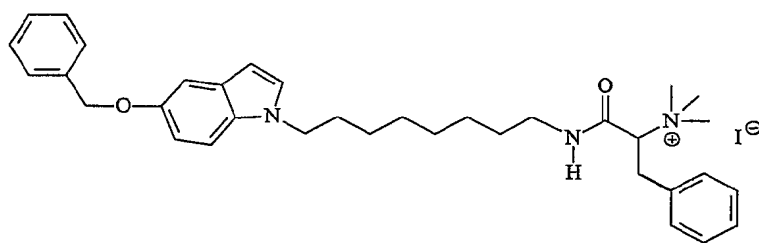
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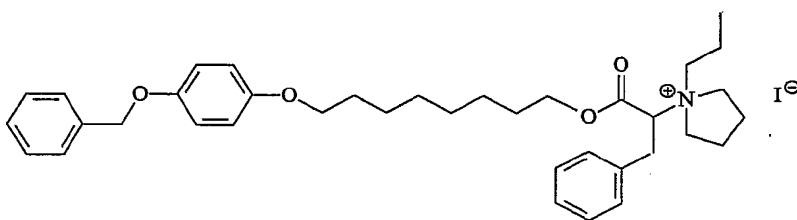


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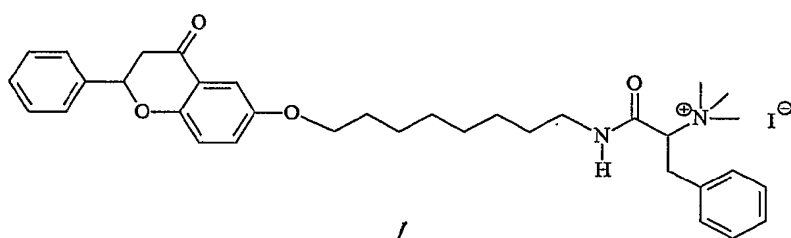
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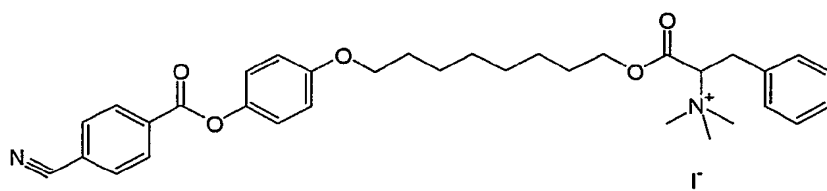


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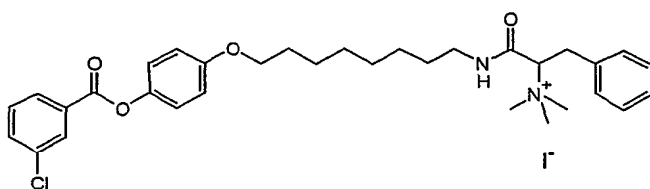


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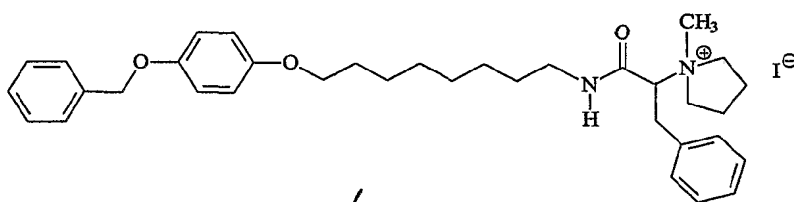
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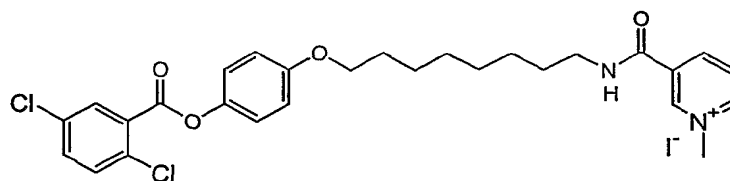


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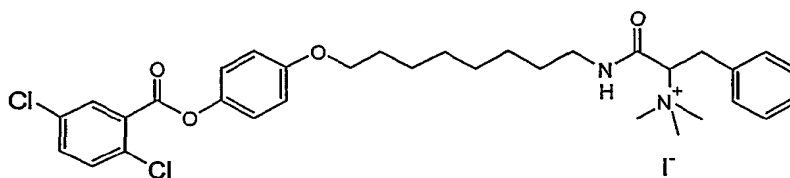


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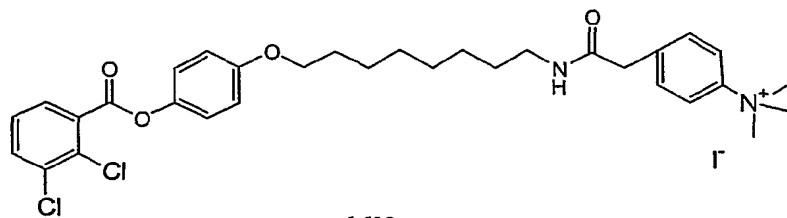
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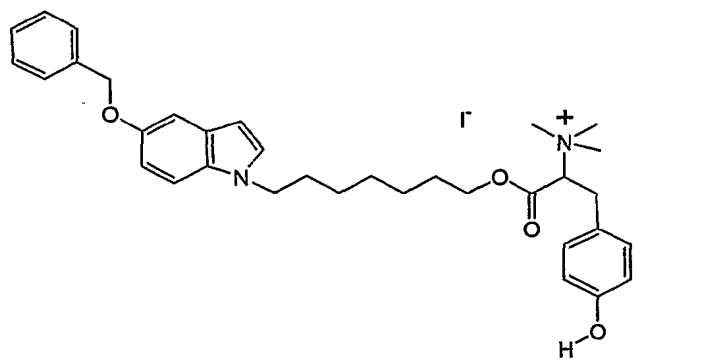


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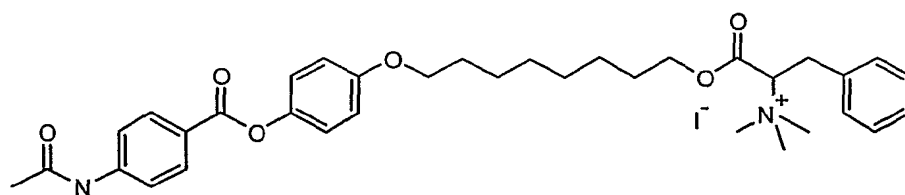
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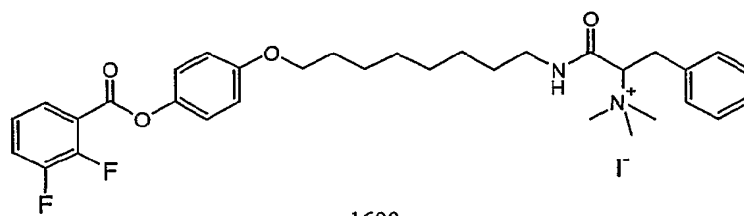
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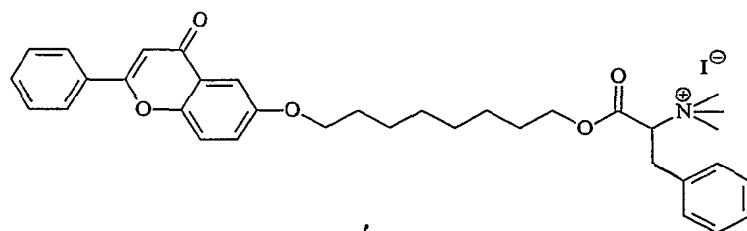


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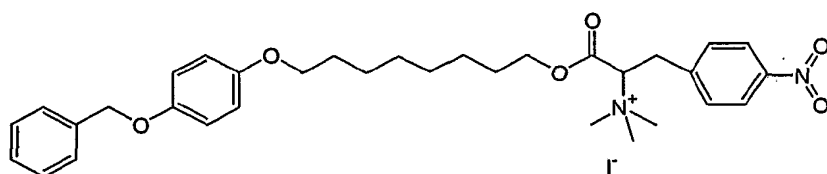


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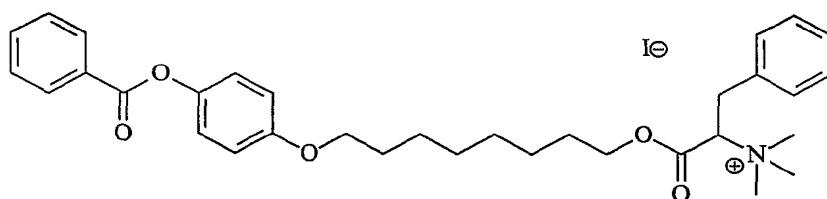
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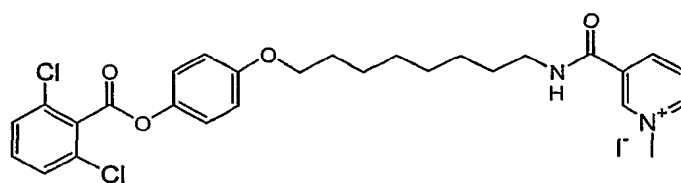
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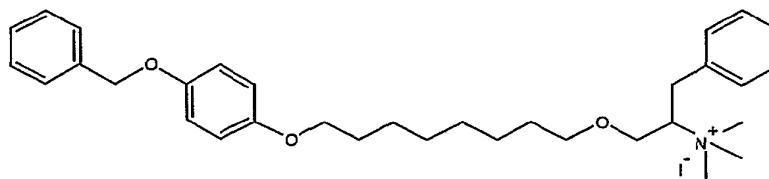


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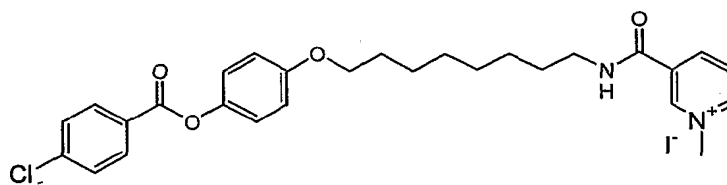
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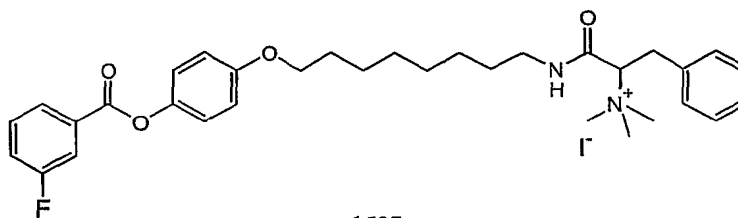
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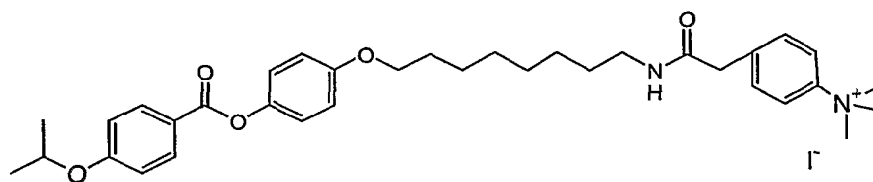
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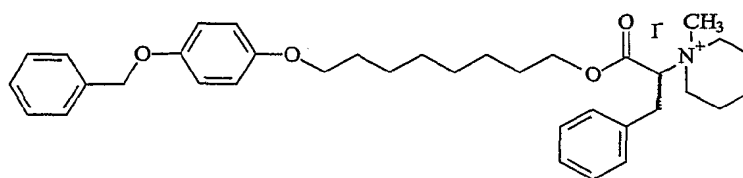
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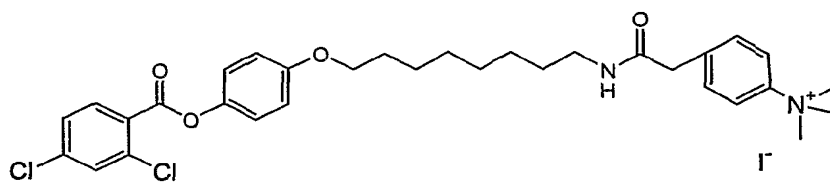
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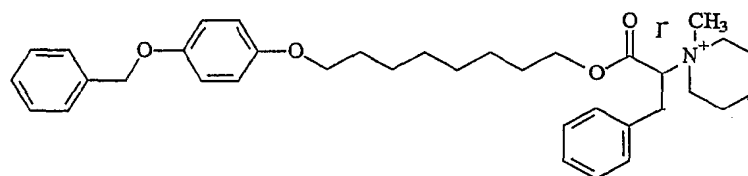
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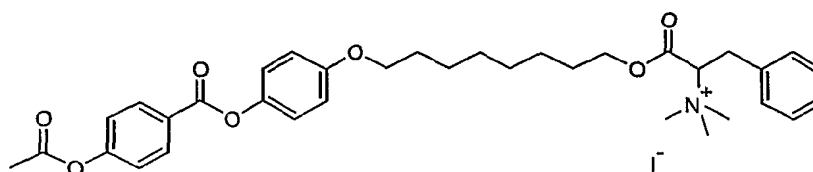


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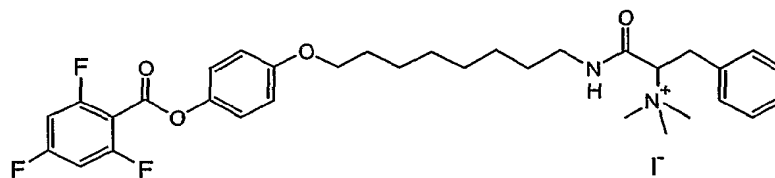
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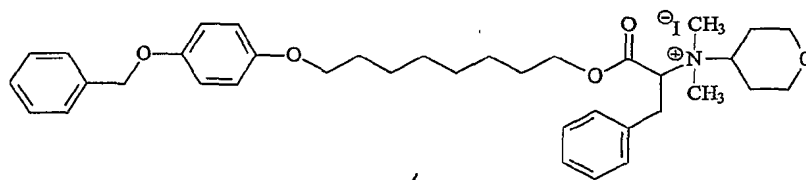


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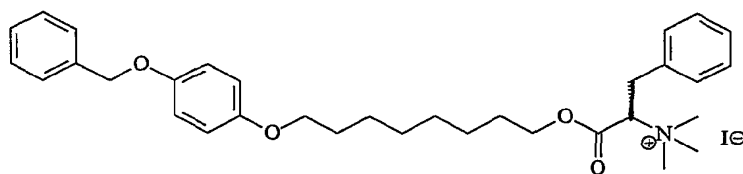


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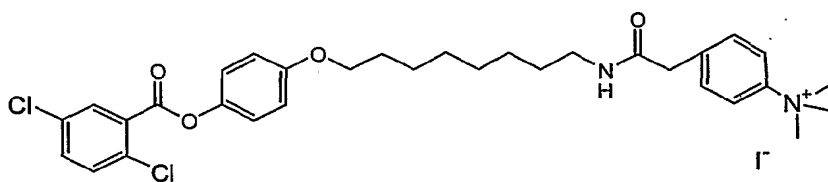


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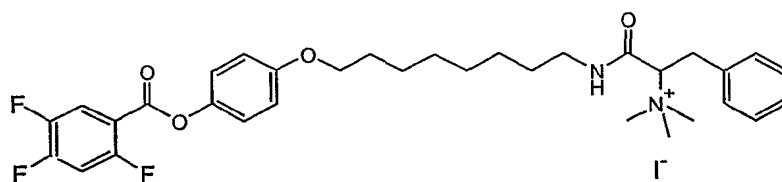
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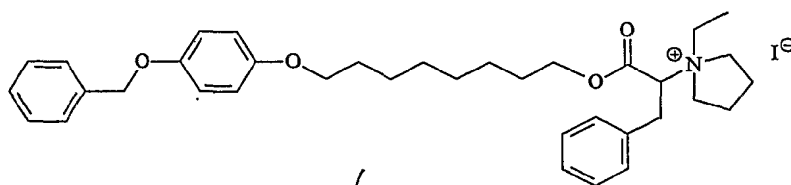
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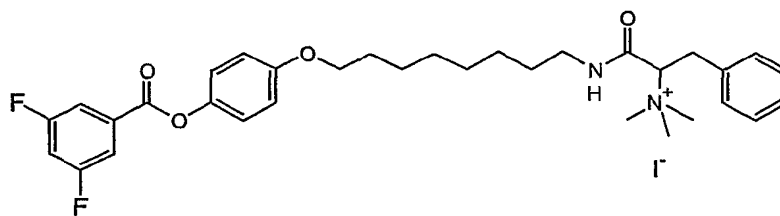


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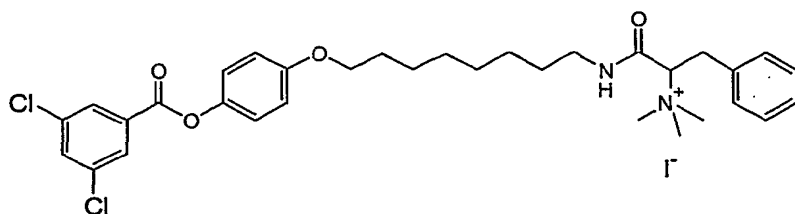


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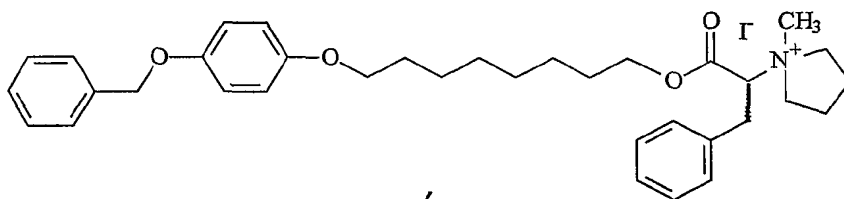


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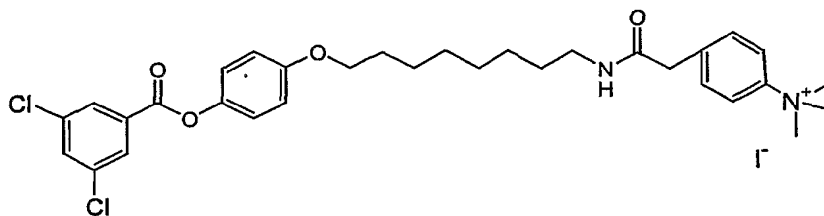


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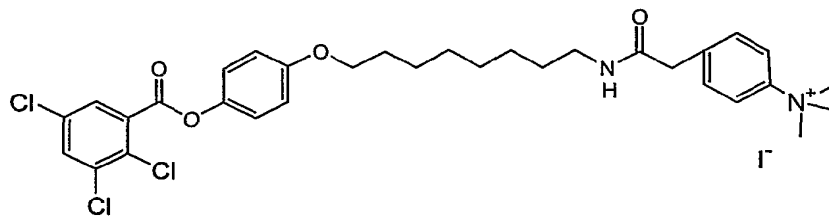
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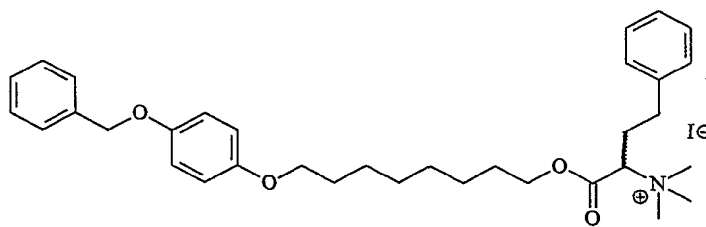
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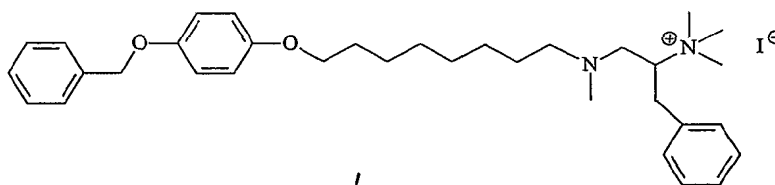
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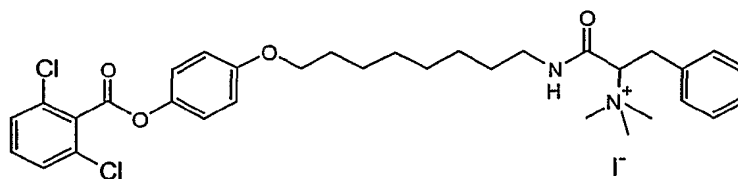
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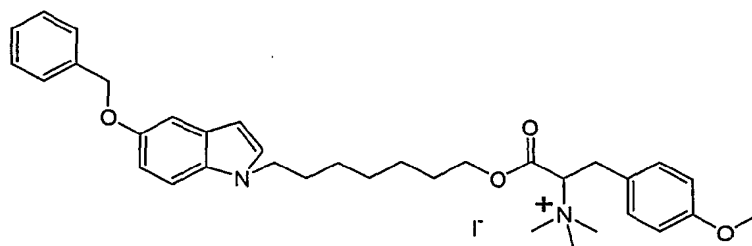


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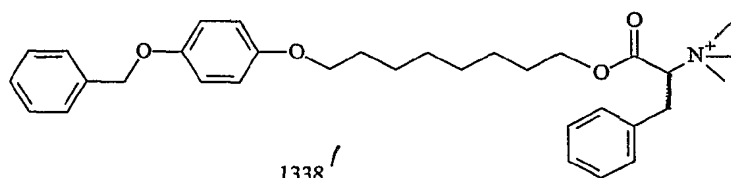
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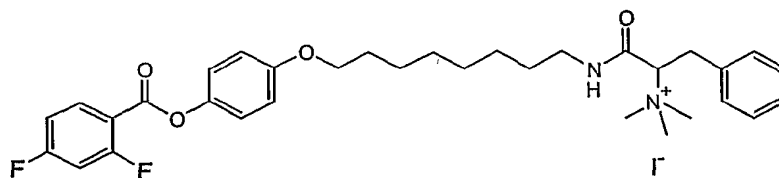


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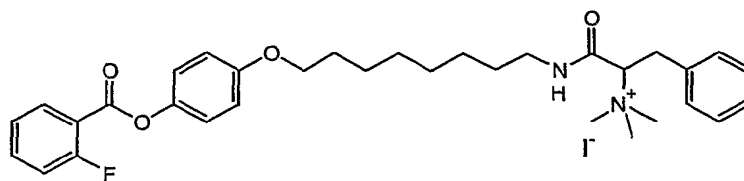


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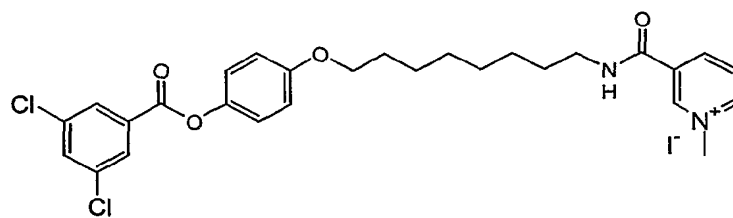
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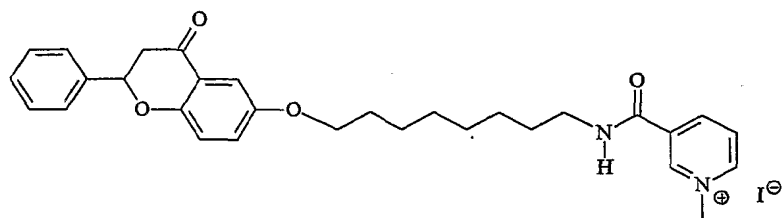
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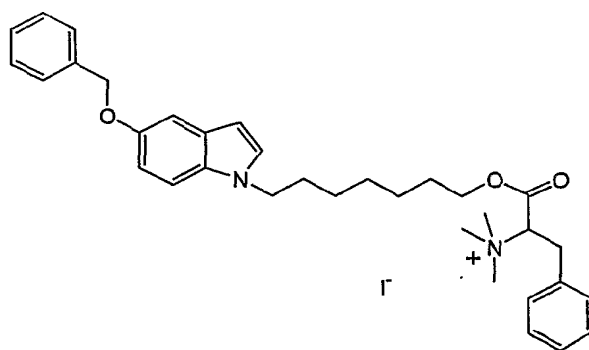


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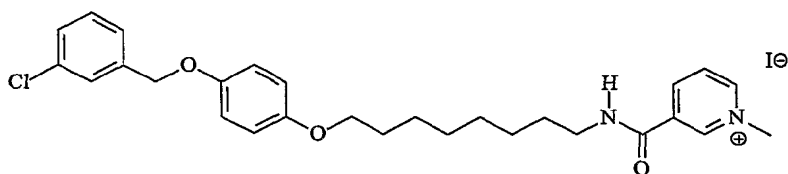
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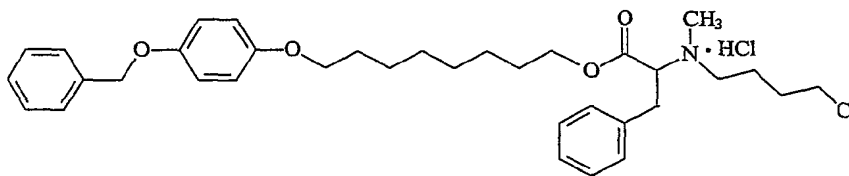
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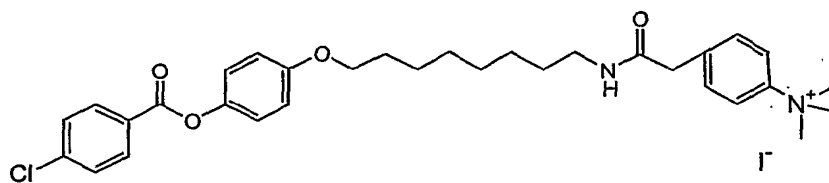


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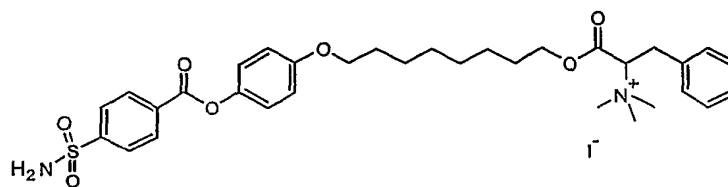


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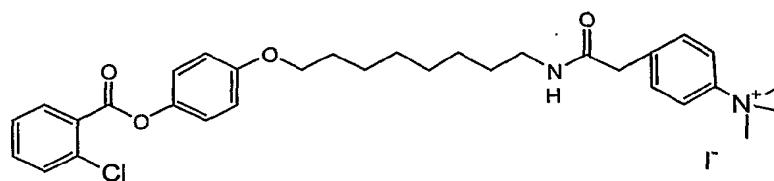


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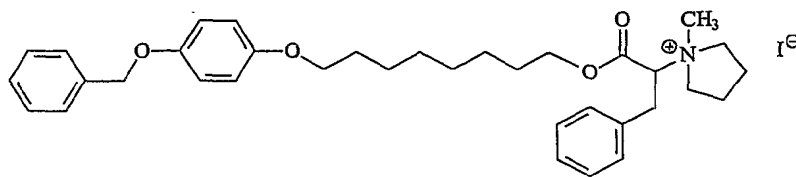


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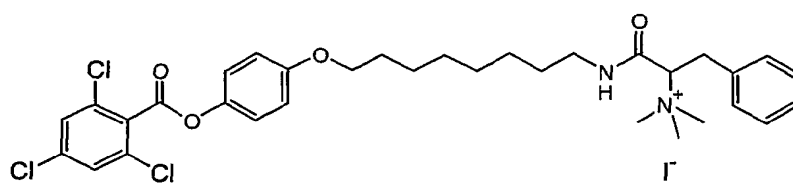
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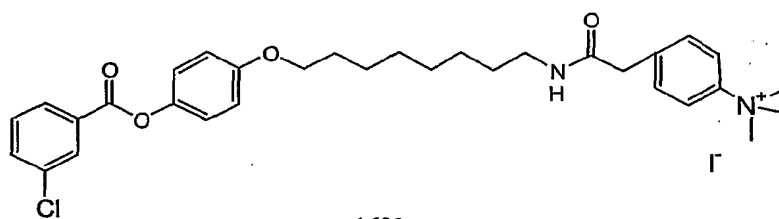


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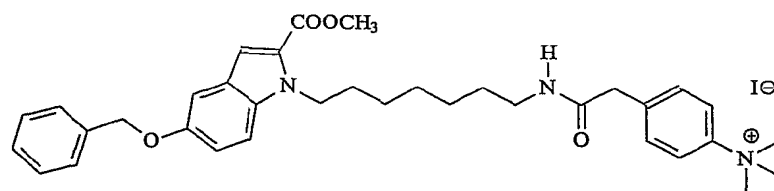
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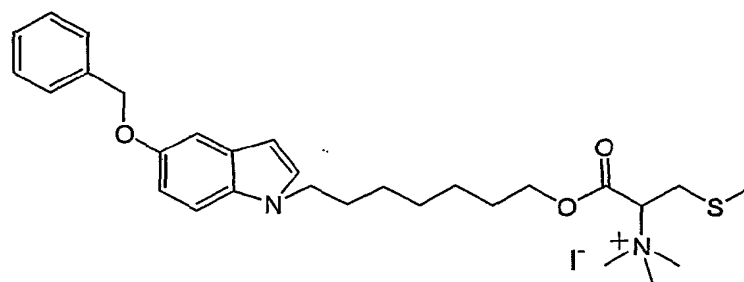
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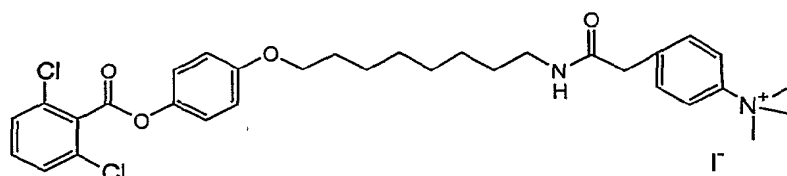


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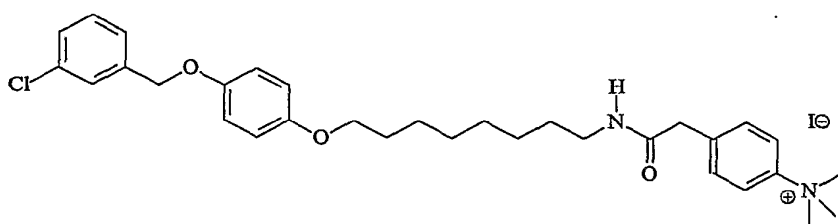
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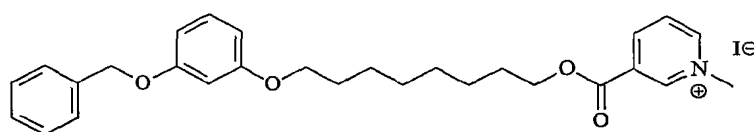


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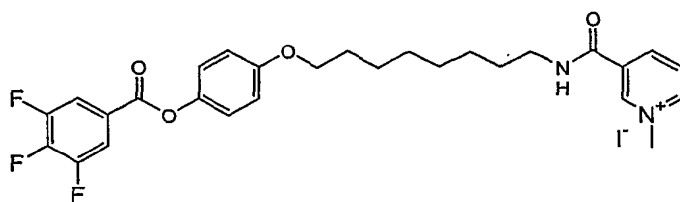


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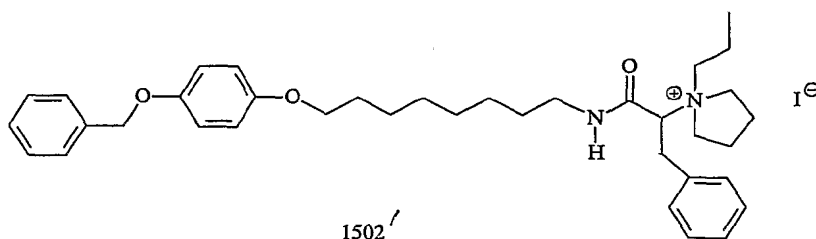


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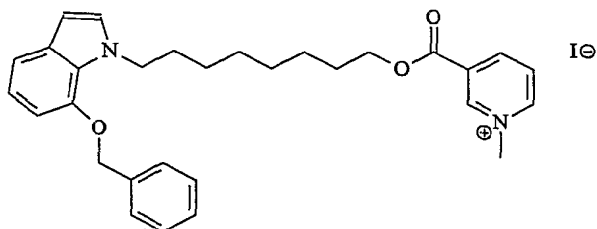


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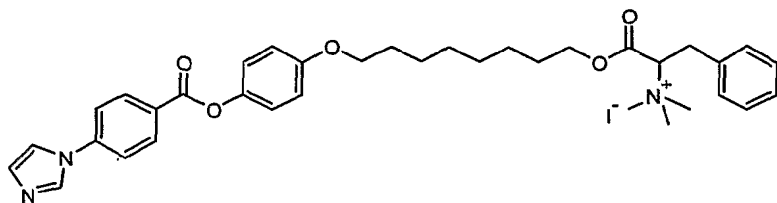
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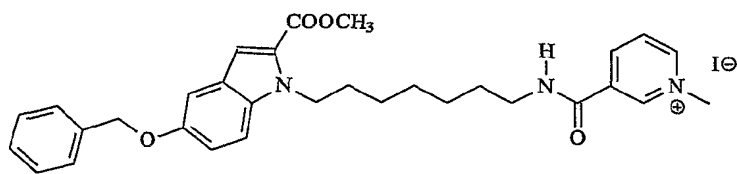


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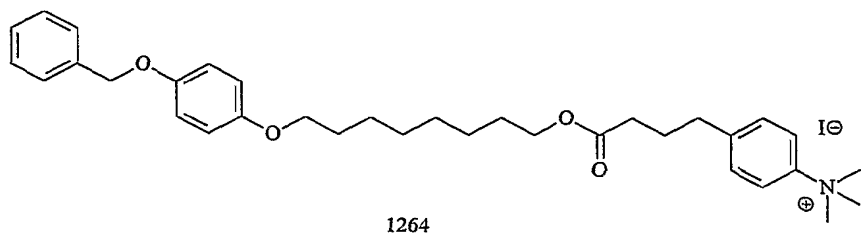


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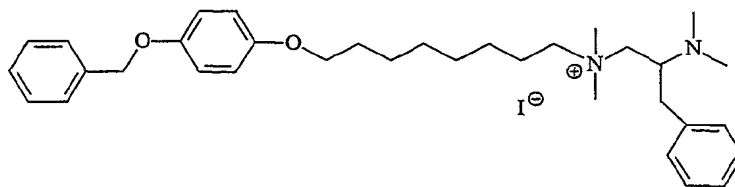
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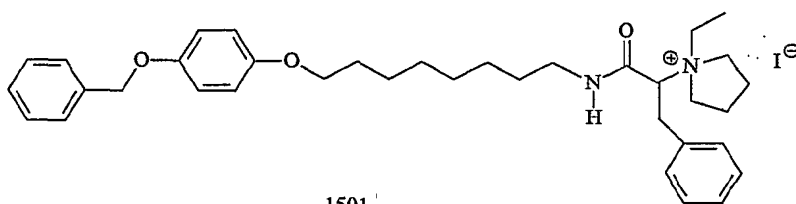


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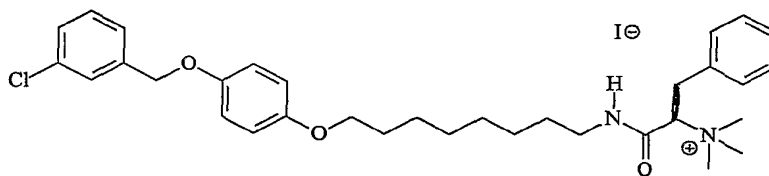
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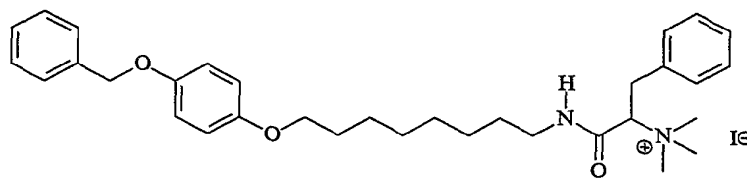
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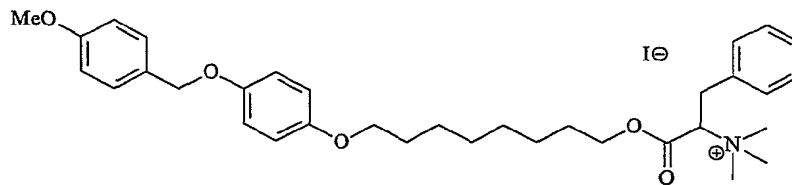


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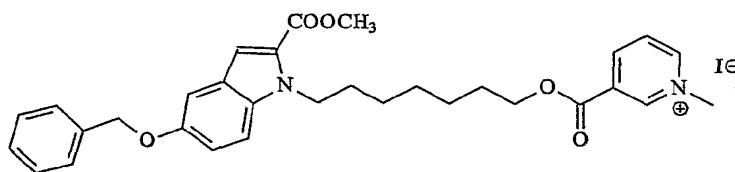


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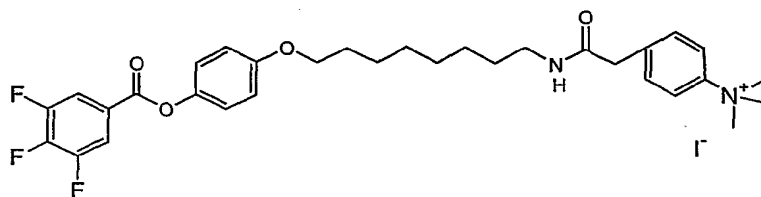


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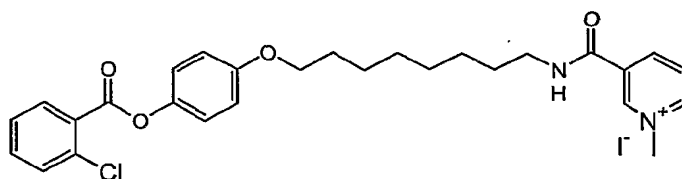
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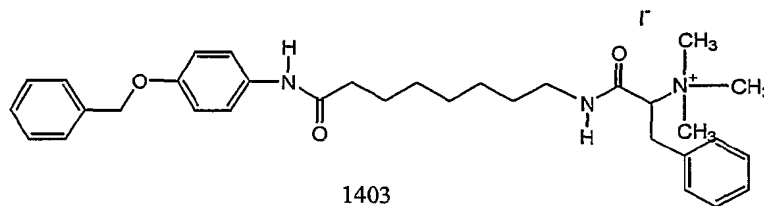


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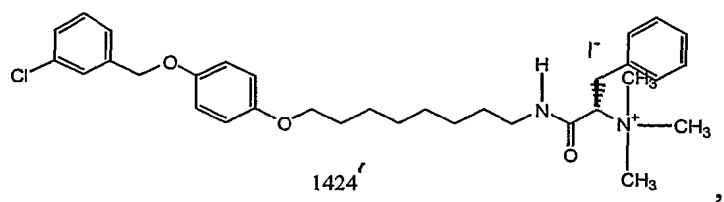


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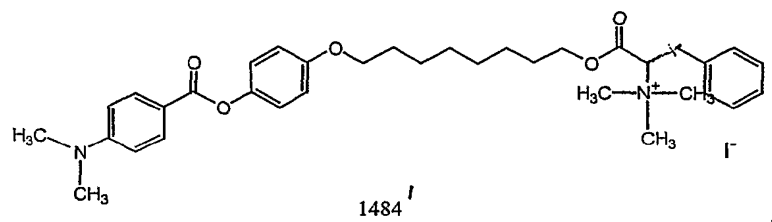
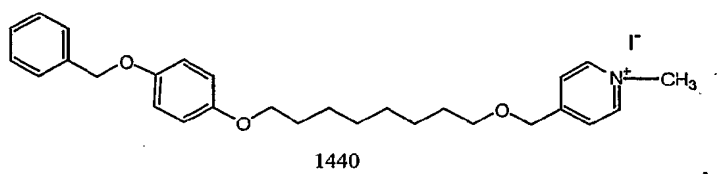


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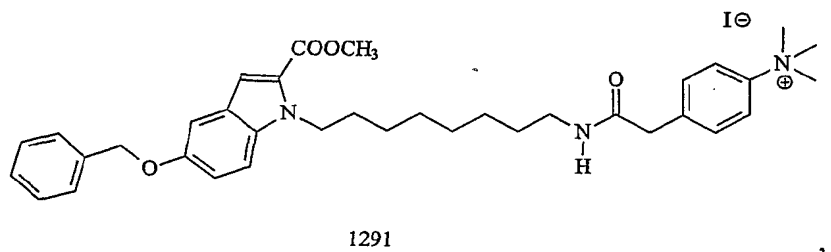
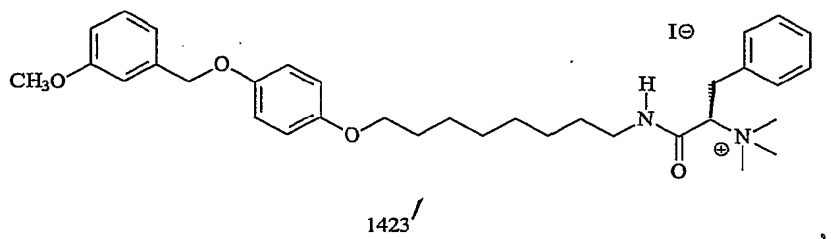
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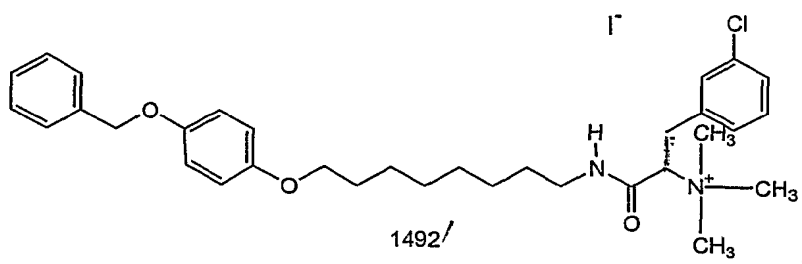
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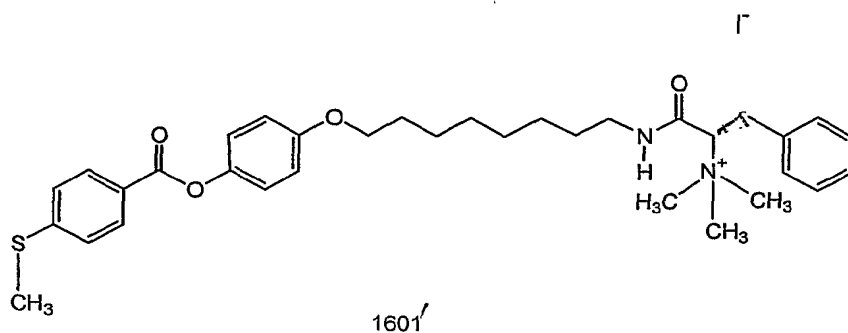
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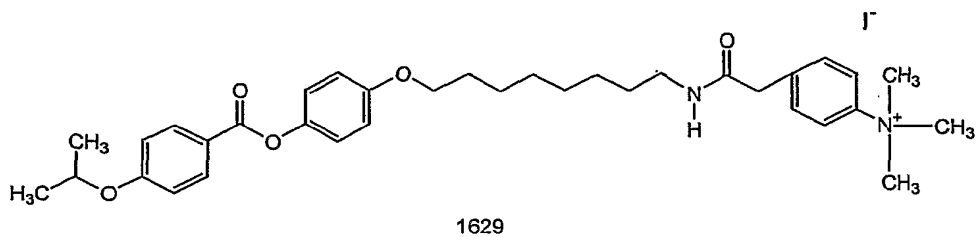
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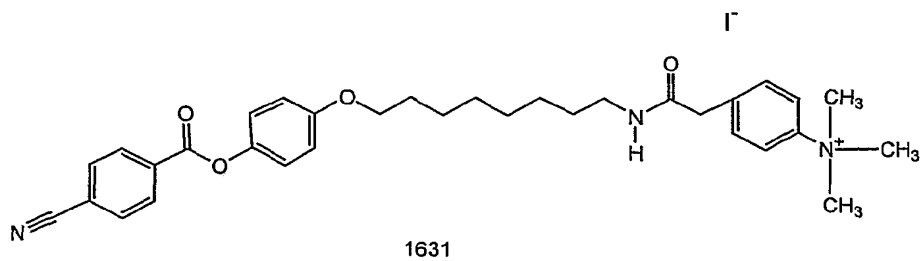
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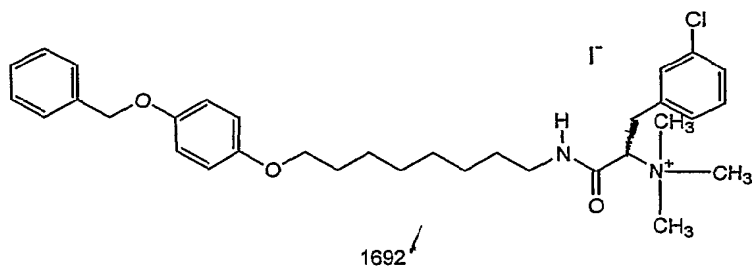


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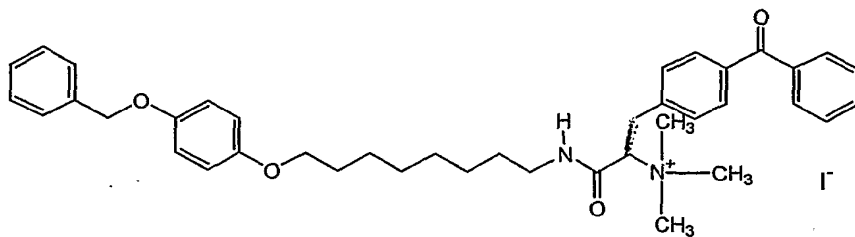
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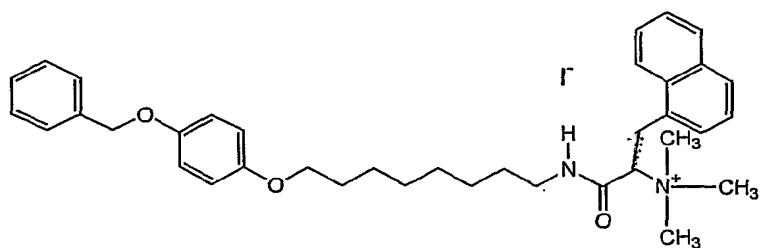
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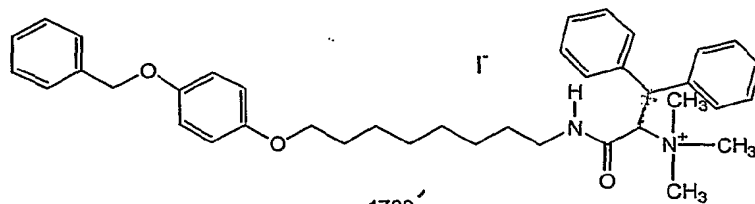


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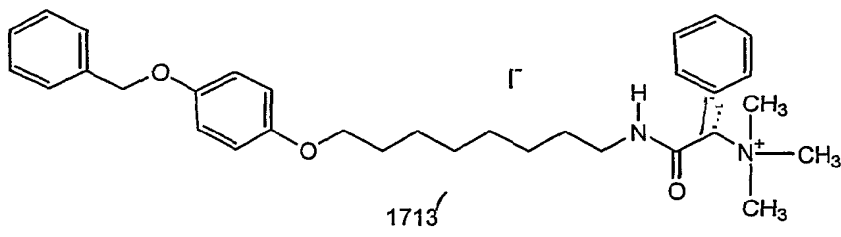


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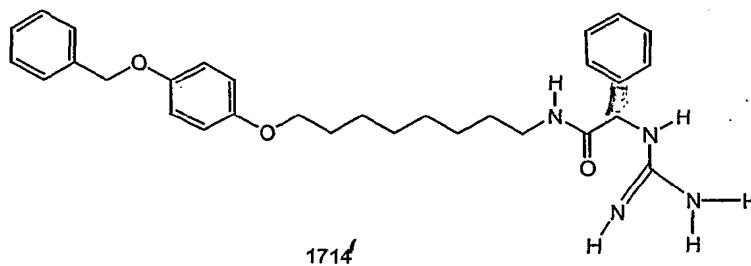


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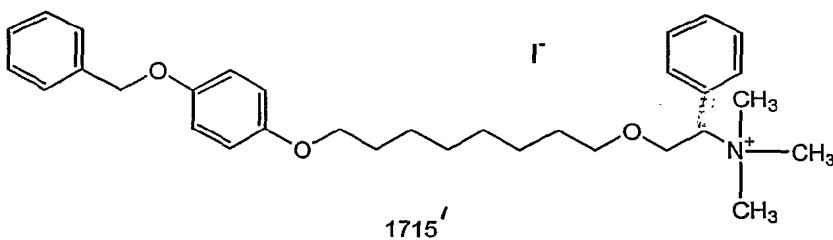
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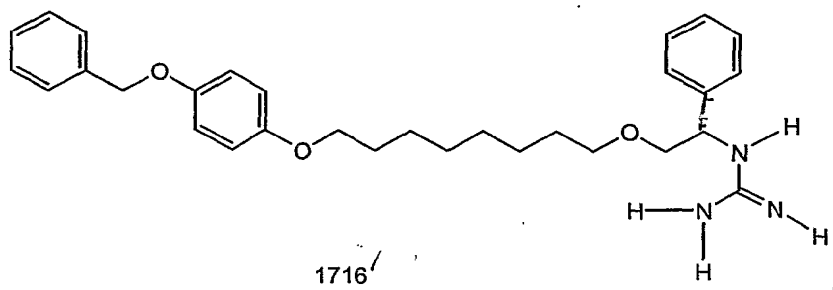
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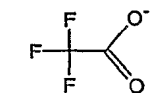
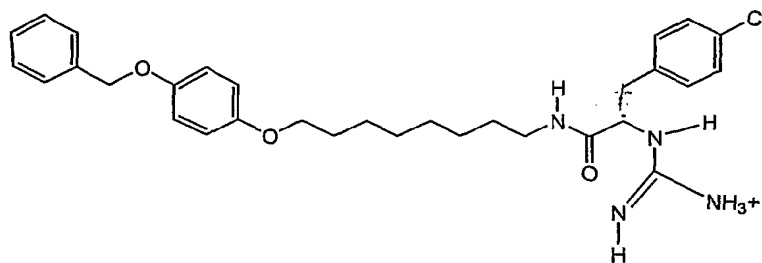
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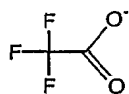
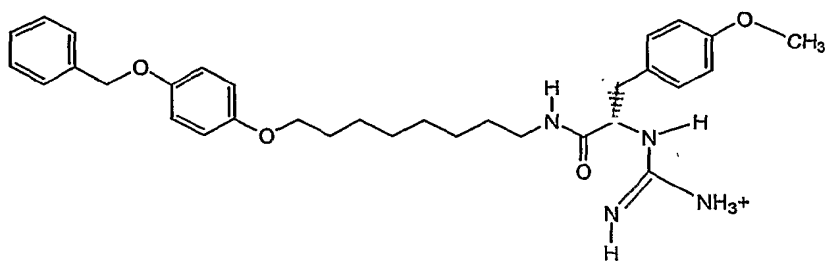


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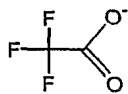
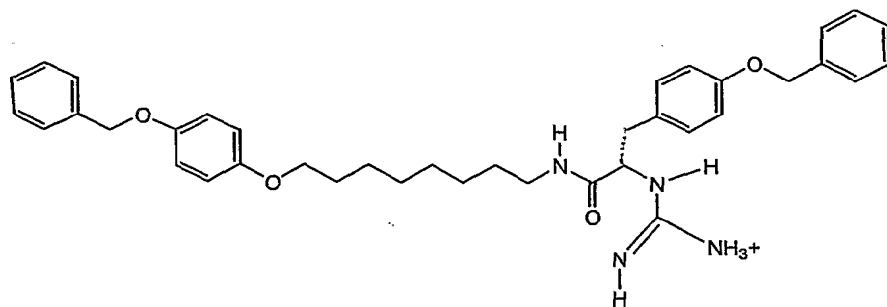


1722'

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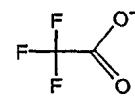
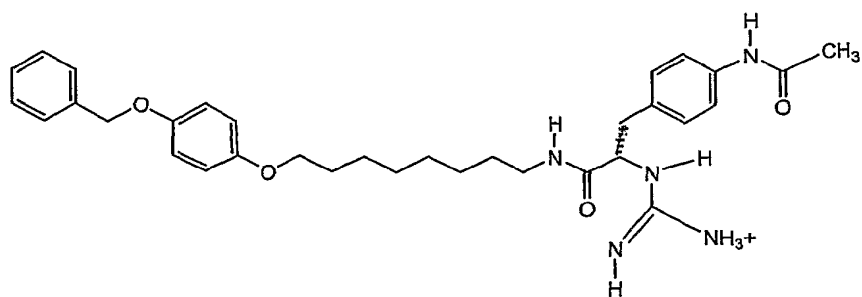
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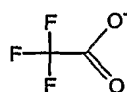
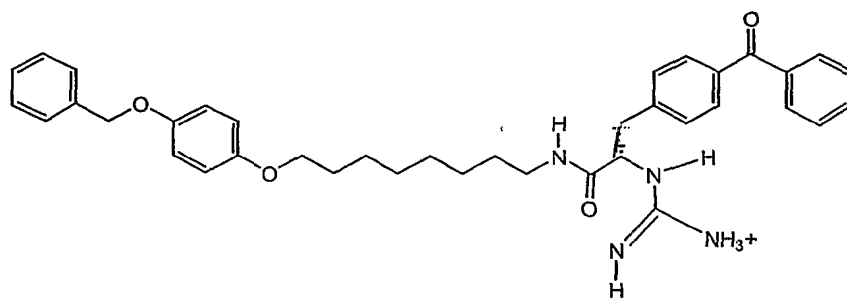
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1728'

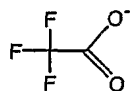
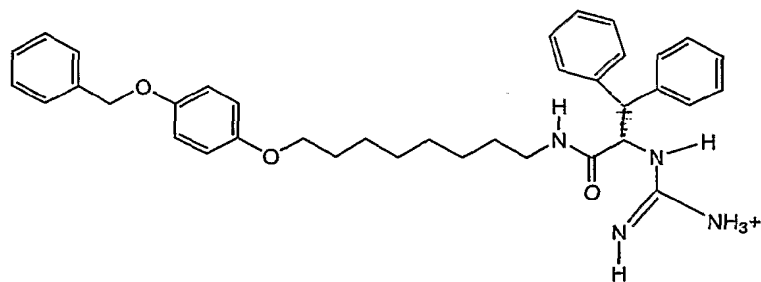
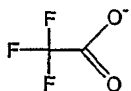
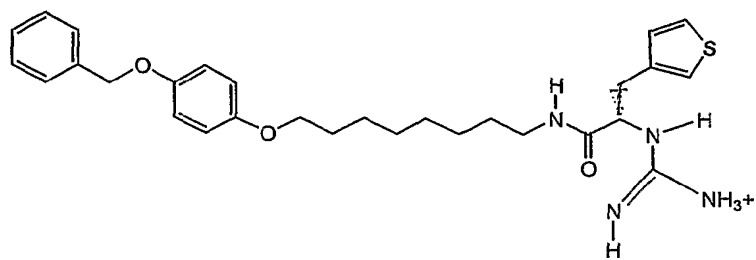
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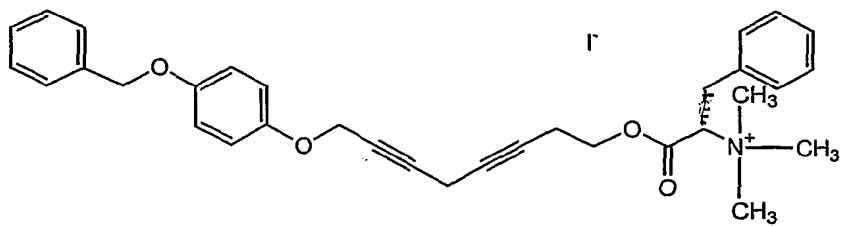
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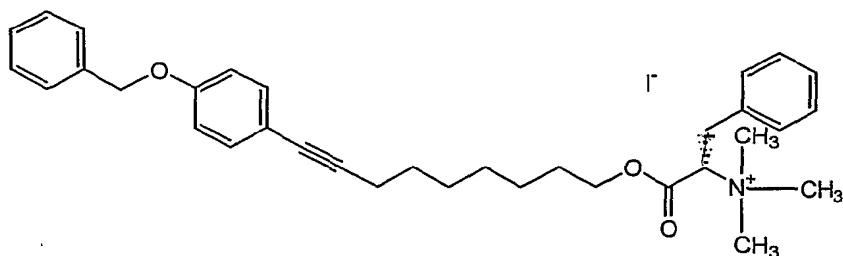
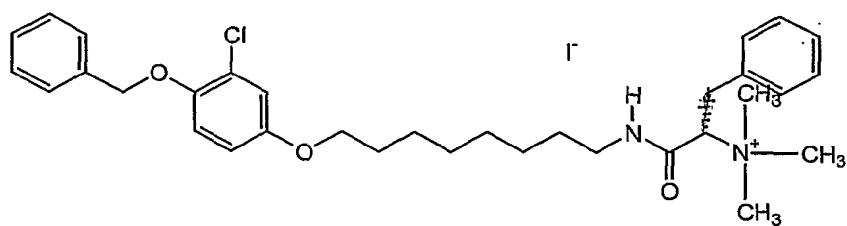
1738^f1741^f

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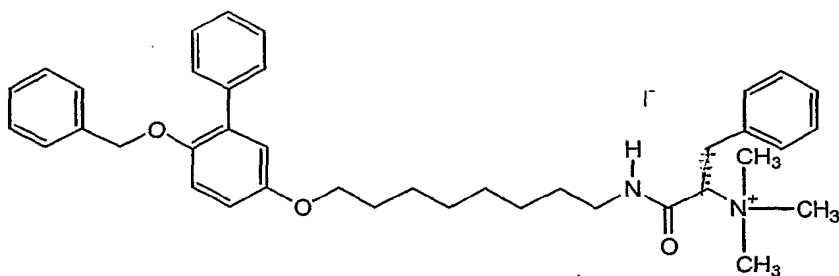
1752^f

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1755^f1758^f

, and



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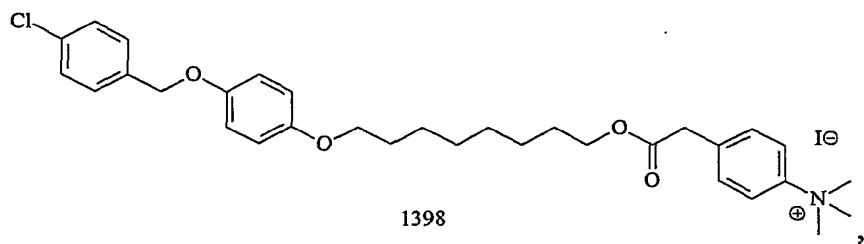
wherein Γ is a pharmaceutically acceptable anion

23. The compound of claim 22, wherein the pharmaceutically acceptable anion is iodide.

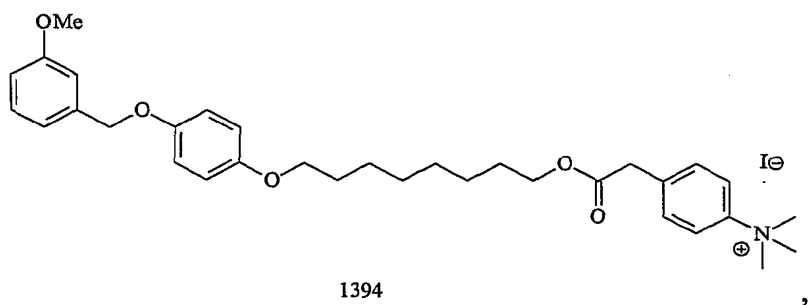
24. A compound of the formula $A-B-(CH_2)_n-O-CO-CH_2-Ph (NMe_3)^+ \Gamma^-$, wherein A is a phenyl or indole, optionally substituted with a benzyloxy group; B is a covalent bond or oxygen atom; n is 1-15; and Γ is a pharmaceutically acceptable anion.

25. The compound of claim 24, selected from the group consisting of

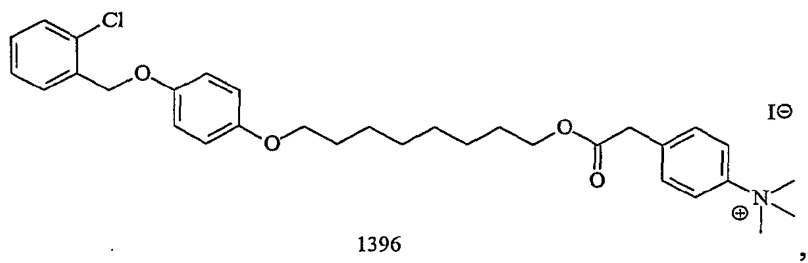
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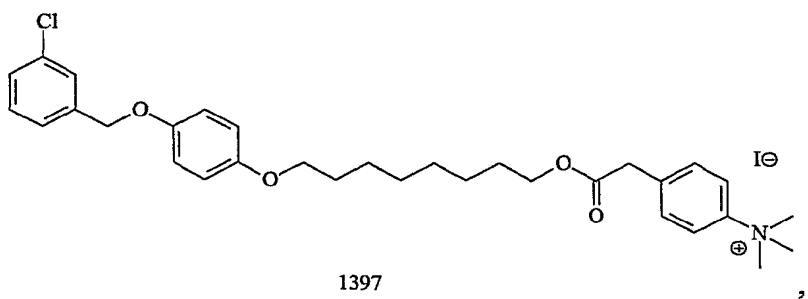
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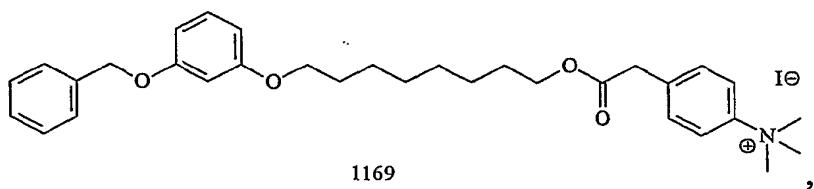
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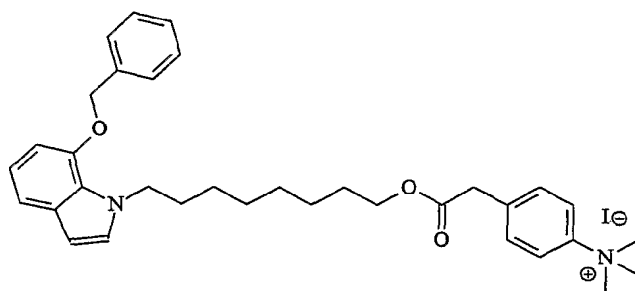


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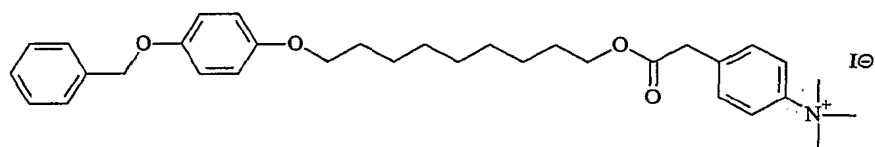


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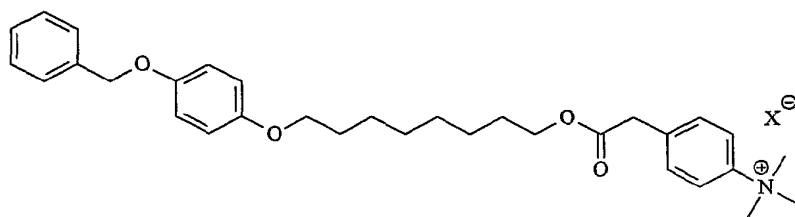
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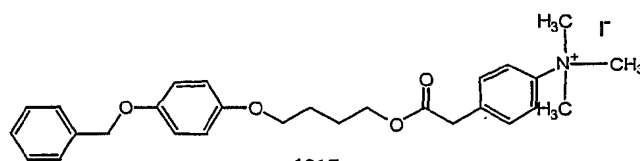
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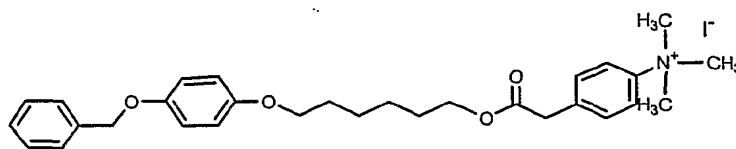
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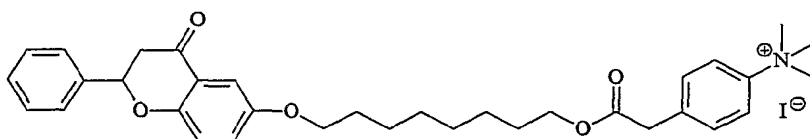


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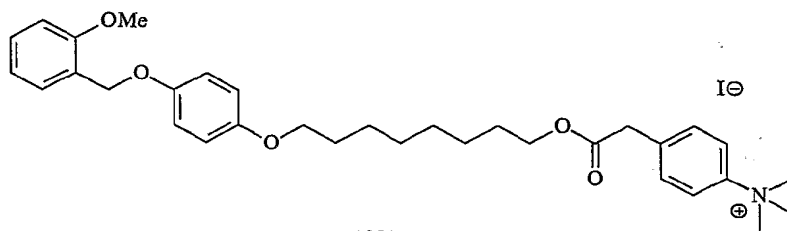


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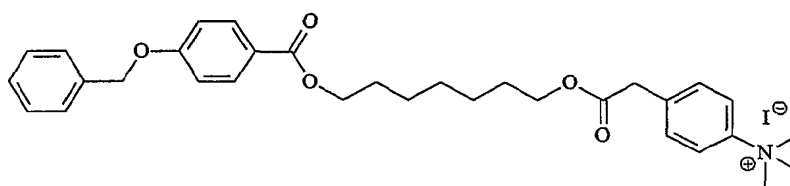
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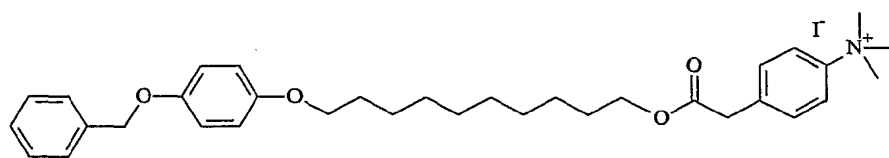
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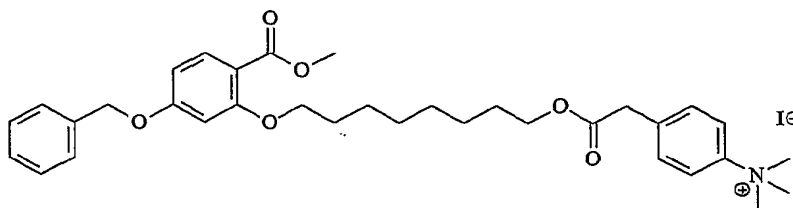
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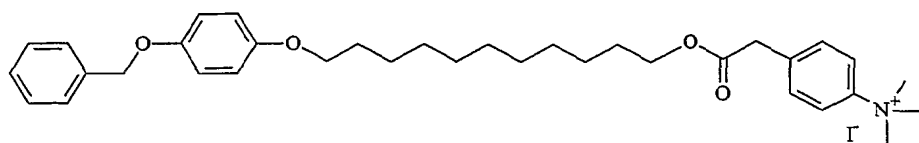
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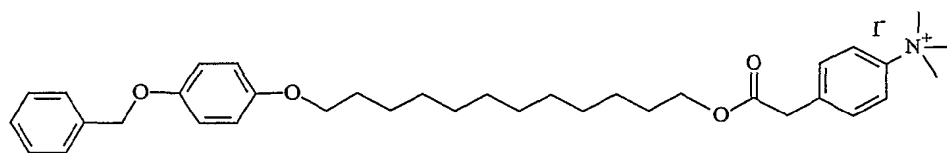


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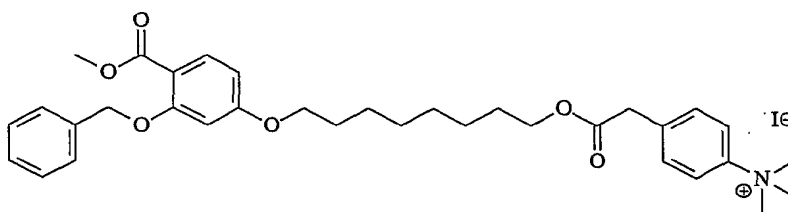
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, and



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5 wherein Γ^- is a pharmaceutically acceptable anion.

26. The compound of claim 25, wherein the a pharmaceutically acceptable anion is iodide.

10 27. A pharmaceutical composition comprising a compound of any of claims 1-26 and a pharmaceutically acceptable carrier.

28. A method for treating or preventing a microbial infection in a mammal comprising administering to said mammal an effective amount of a compound of any of claims 1-26.

15 29. A method for treating or preventing a microbial infection in a mammal comprising administering to said mammal an effective amount of a compound that inhibits the enzymatic activity of the microbial NAD synthetase.

30. A method for preparing a compound of the formula A:

20
$$\text{Ar}_1\text{-X-Ar}_2\text{-O-(CH}_2\text{)}_n\text{-NHCO-Q}_1\text{Ar}_3 \quad (\text{A})$$

wherein Ar_1 , Ar_2 , and Ar_3 are independently aryl or heteroaryl, optionally substituted with one or more substituents selected from the group consisting of $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $\text{C}_1\text{-C}_6$ alkoxy $\text{C}_1\text{-C}_6$ alkyl, halo, amino, $\text{C}_1\text{-C}_6$ alkylamino, $\text{C}_1\text{-C}_6$ dialkylamino, $\text{C}_1\text{-C}_6$ trialkylamino, $\text{C}_1\text{-C}_6$ alkylamino $\text{C}_1\text{-C}_6$ alkyl,

C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide, hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆ alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino, sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino, mercaptyl, and heterocyclyl; optionally, a ring nitrogen atom of heteroaryl Ar₁, Ar₂, or Ar₃ may be quaternized;

X is selected from the group consisting of a covalent bond, (CH₂)_mO, O(CH₂)_m, (CH₂O)_m, (OCH₂)_m, (CH₂CH₂O)_m, (OCH₂CH₂)_m, C(=O)O, OC(=O), OC(=O)O, (CH₂)_mS, S(CH₂)_m, (CH₂S)_m, (SCH₂)_m, NH, NR, ⁺NR₂, C(=O)NH, C(=O)NR, NHC(=O), NRC(=O), CH(OH), and CH(OR), wherein R is C₁-C₆ alkyl and m is 0-5;

Q₁ is (i) a C₁-C₆ alkylenyl, C₁-C₆ alkylenyl carbonyloxy C₁-C₆ alkyl, or C₁-C₆ alkylenyl carbonylamino C₁-C₆ alkyl group, optionally having a substituent selected from the group consisting of amino, C₁-C₆ alkylamino, C₁-C₆ haloalkylamino, C₁-C₆ haloalkyl C₁-C₆ alkyl amino, C₁-C₆ hydroxyalkylamino, C₁-C₆ hydroxyalkyl C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, and a heterocyclic containing a nitrogen atom which may be optionally quaternized;

and n is from 1 to 15;

comprising (i) providing a compound of the formula B:

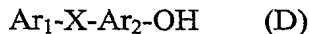


and (ii) reacting the compound of formula B with a compound of formula C:

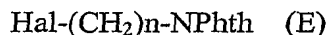


wherein Q₁ is optionally protected.

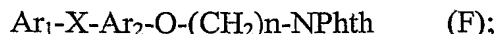
31. The method of claim 30, wherein the compound of formula B is prepared by reacting a compound of formula D:



with a compound of formula E:



wherein "Hal" stands for a halogen atom and "NPhth" stands for phthalidimide linked to (CH₂)_n at the nitrogen atom, to obtain a compound of formula F:



and hydrolyzing the compound of formula F.

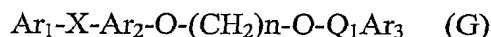
32. The method of claim 30 or 33, wherein n is from 7 to 13.

5 33. The method of claim 30, wherein Ar₁, Ar₂, and Ar₃ are phenyl.

34. The method of claim 30, wherein X is CH₂O.

35. The method of claim 30, wherein Q₁ is a C₁-C₆ alkylene, optionally having a
 10 substituent selected from the group consisting of amino, C₁-C₆ alkylamino, C₁-C₆
 haloalkylamino, C₁-C₆ haloalkyl C₁-C₆ alkyl amino, C₁-C₆ hydroxyalkylamino, C₁-C₆
 hydroxyalkyl C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, and a
 heterocyclic containing a nitrogen atom which may be optionally quaternized.

15 36. A method for preparing a compound of the formula G:



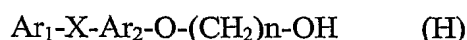
wherein Ar₁, Ar₂, and Ar₃ are independently aryl or heteroaryl, optionally
 substituted with one or more substituents selected from the group consisting of C₁-C₆ alkyl,
 C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ alkoxy C₁-C₆ alkyl, halo, amino,
 20 C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ trialkylamino, C₁-C₆ alkylamino C₁-C₆ alkyl,
 C₁-C₆ dialkylamino C₁-C₆ alkyl, C₁-C₆ trialkylamino C₁-C₆ alkyl, azido, amine oxide,
 hydroxy, carboxyl, C₁-C₆ alkylcarbonyl, C₁-C₆ alkylcarbonyl C₁-C₆ alkyl, C₁-C₆
 alkylcarbonyloxy, C₁-C₆ alkylcarbonyloxy C₁-C₆ alkyl, C₁-C₆ alkyloxycarbonyl C₁-C₆
 alkyl, C₁-C₆ alkyloxycarbonyl, C₁-C₆ alkylthio, nitro, nitrosyl, cyano, hydroxylamino,
 25 sulfonamido, C₁-C₆ dialkyl sulfonamido, C₁-C₆ alkylcarbonylamino, formyl, formylamino,
 mercaptyl, and heterocyclyl; optionally, a ring nitrogen atom of heteroaryl Ar₁, Ar₂, or Ar₃
 may be quaternized;

X is selected from the group consisting of a covalent bond, (CH₂)_mO, O(CH₂)_m,
 (CH₂O)_m, (OCH₂)_m, (CH₂CH₂O)_m, (OCH₂CH₂)_m, C(=O)O, OC(=O), OC(=O)O, (CH₂)_mS,
 30 S(CH₂)_m, (CH₂S)_m, (SCH₂)_m, NH, NR, ⁺NR₂, C(=O)NH, C(=O)NR, NHC(=O), NRC(=O),
 CH(OH), and CH(OR), wherein R is C₁-C₆ alkyl and m is 0-5;

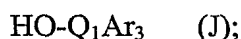
Q_1 is (i) a C_1 - C_6 alkylene, C_1 - C_6 alkylene carbonyloxy C_1 - C_6 alkyl, or C_1 - C_6 alkylene carbonylamino C_1 - C_6 alkyl group, optionally having a substituent selected from the group consisting of amino, C_1 - C_6 alkylamino, C_1 - C_6 haloalkylamino, C_1 - C_6 haloalkyl C_1 - C_6 alkyl amino, C_1 - C_6 hydroxyalkylamino, C_1 - C_6 hydroxyalkyl C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 trialkylamino, and a heterocyclic containing a nitrogen atom which may be optionally quaternized;

and n is from 1 to 15;

comprising (i) providing a compound of the formula H:

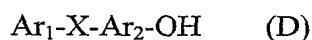


and (ii) reacting the compound of formula H with a compound of formula J:

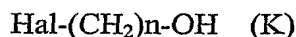


wherein Q_1 is optionally protected.

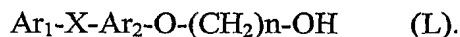
37. The method of claim 36, wherein the compound of formula H is prepared by reacting a compound of formula D:



with a compound of formula K:



wherein "Hal" stands for a halogen atom, to obtain a compound of formula L:



38. The method of claim 36 or 37, wherein n is from 7 to 13.

39. The method of claim 38, wherein Ar_1 , Ar_2 , and Ar_3 are phenyl.

40. The method of any of claims 36-39, wherein X is CH_2O .

41. The method of claim 36 or 37, wherein Q_1 is a C_1 - C_6 alkylene, optionally having a substituent selected from the group consisting of amino, C_1 - C_6 alkylamino, C_1 - C_6 haloalkylamino, C_1 - C_6 haloalkyl C_1 - C_6 alkyl amino, C_1 - C_6 hydroxyalkylamino, C_1 - C_6 hydroxyalkyl C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 trialkylamino, and a heterocyclic containing a nitrogen atom which may be optionally quaternized.

42. A method of killing a prokaryote comprising contacting the prokaryote with an effective amount of the compound of any of claims 1-26 to reduce or eliminate the production of NAD.

5

43. A method of decreasing prokaryotic growth, comprising contacting the prokaryote with an effective amount of a compound of any of claims 1-26 to reduce or eliminate the production of NAD.

10 44. The method of claim 42 or 43, wherein the prokaryote is a bacterium.

45. The method of claim 44, wherein the bacterium is a gram negative or a gram positive bacterium.

15 46. The method of claim 42 or 43, wherein the prokaryote is an antibiotic resistant strain of a bacterium.

47. A disinfecting, sterilizing, or decontaminating composition comprising a compound of any of claims 1-26.

20

48. A method of disinfecting, sterilizing, or decontaminating a material in need thereof, comprising contacting the material with a compound of any of claims 1-26.

25 49. A method of killing a fungus comprising contacting the fungus with an amount of a compound of any of claims 1-26 to reduce or eliminate the production of NAD.

50. A method of decreasing fungus growth comprising contacting the fungus with an effective amount of a compound of any of claims 1-26 to reduce or eliminate the production of NAD.

30

51. A method of increasing production of a food animal comprising administering to the food animal an effective amount of a compound of any of claims 1-26 to inhibit the NAD synthetase of a microbe capable of infecting the food animal.

5 52. A method for the treatment or prevention of infection by a spore-forming bacterium in an animal comprising contacting an environment of the animal with an effective amount of a compound of any of claims 1-26 to inhibit the NAD synthetase of the spore-forming bacterium.

10 53. A method of killing the vegetative cell of a spore-forming bacterium in an environment comprising treating the environment with an effective amount of a compound of any of claims 1-26 to inhibit the NAD synthetase of the bacterium.

15 54. A method of treating or preventing a microbial infection or disease in a plant comprising contacting the plant or an environment of the plant with an effective amount of a compound of any of claims 1-26 to inhibit the NAD synthetase of the microbe.

20 55. A method for a treating or preventing harm to a plant due to a pest comprising contacting the plant, or an environment thereof, with a pesticidal effective amount of a compound of any of claims 1-26 to inhibit the NAD synthetase of a pest.

25 56. A method of controlling insect population in an environment comprising contacting the environment with an effective amount of a compound of any of claims 1-26 to inhibit the NAD synthetase of the insect.

57. A method for combating agroterrorism involving an infective agent on an object comprising treating the object with an amount of a compound effective to inhibit the NAD synthetase of the infective agent.

30 58. The method of claim 57, wherein the object is an animal, crop, or soil.

59. The method of claim 57, wherein the infective agent is a fungus.

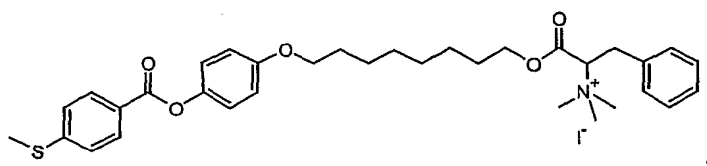
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60. The method of claim 57, wherein the infective agent is a bacterium.

61. A method for combating agroterrorism involving an infective agent on an object
5 comprising treating the object with an amount of a compound effective to inhibit the NAD
synthetase of the infective agent, wherein the compound is a compound of any of claims 1-
26.

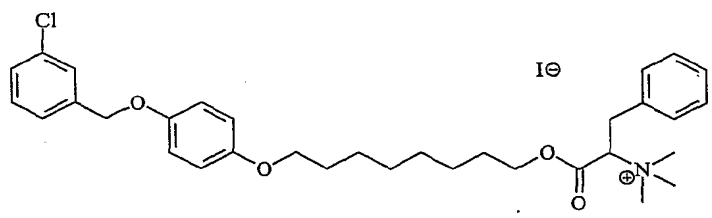
62. The compound of claim 22, which is selected from the group consisting of:

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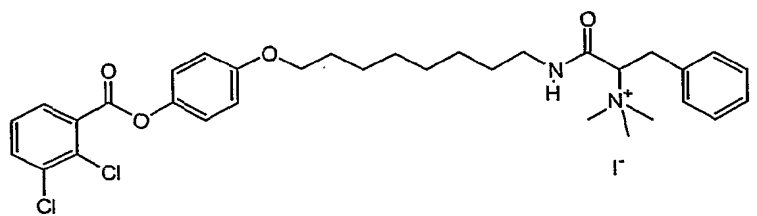
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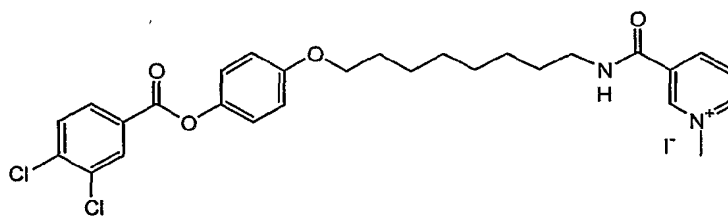
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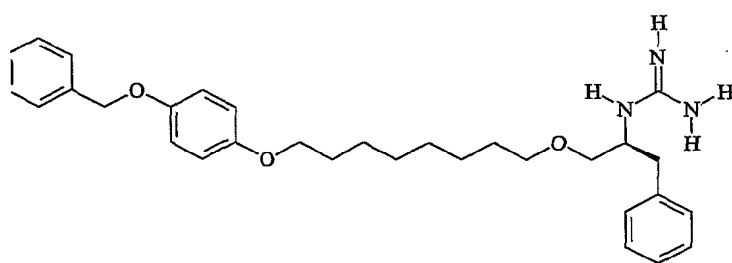


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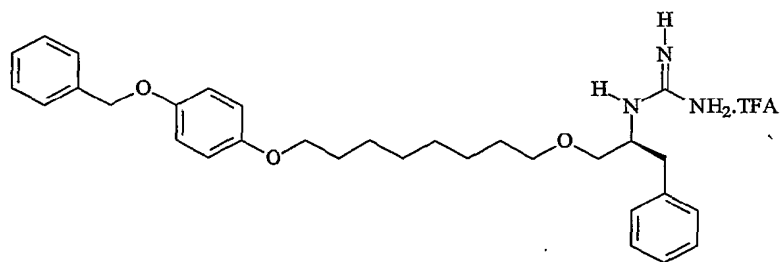


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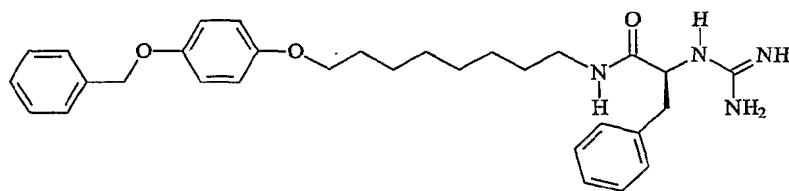
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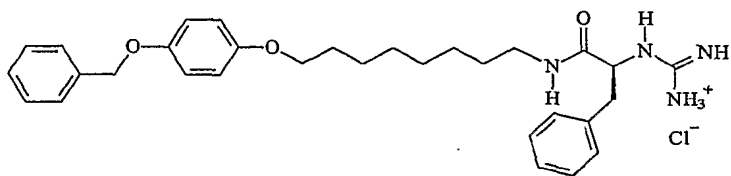
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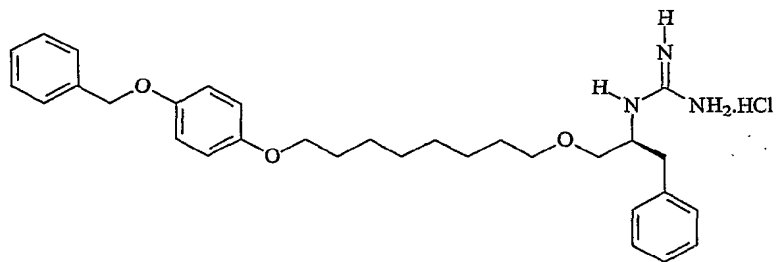
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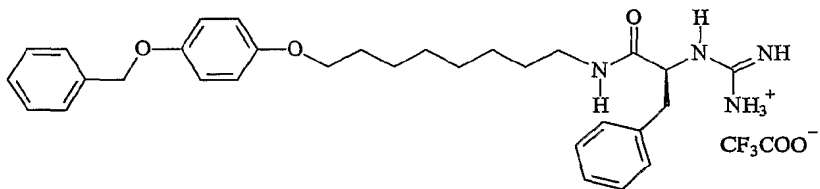


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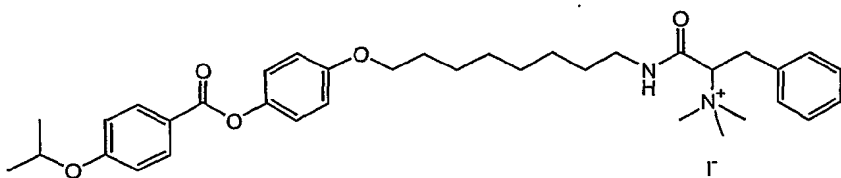
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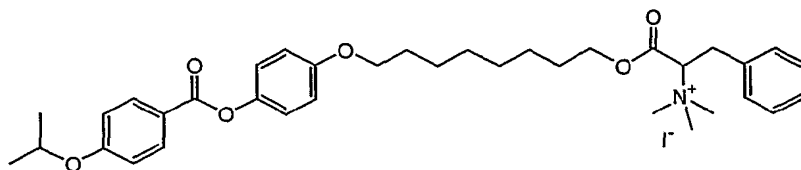


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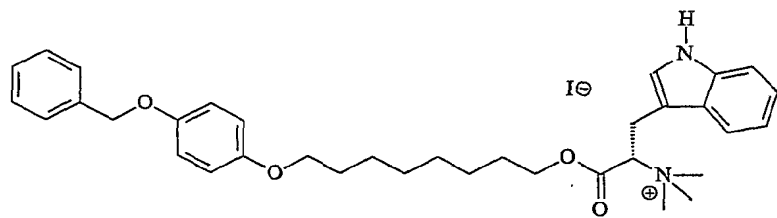
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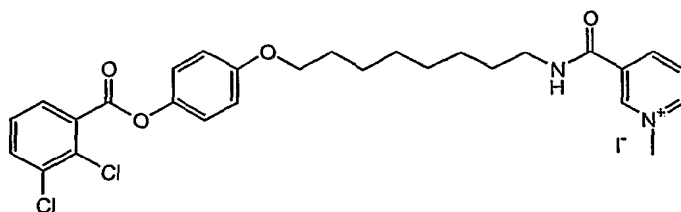
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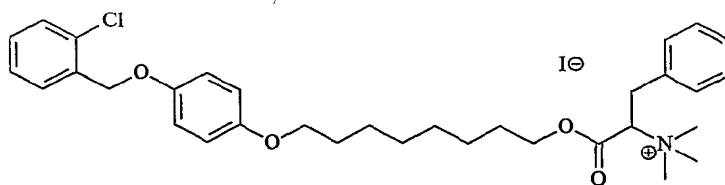


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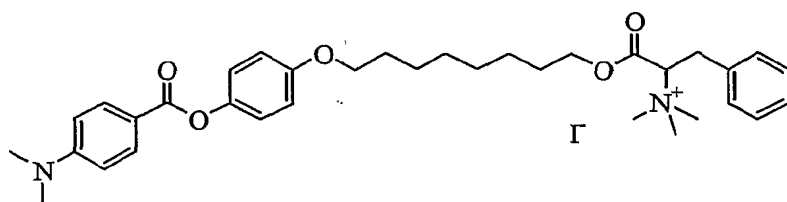
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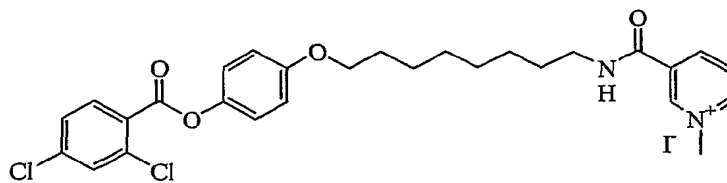
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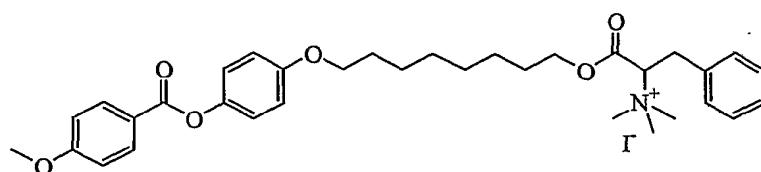


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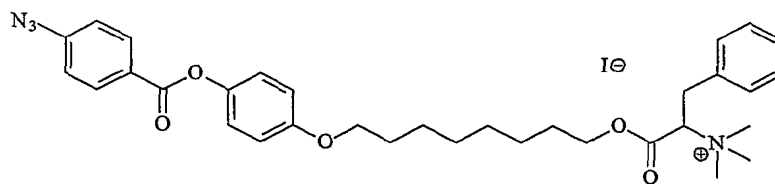
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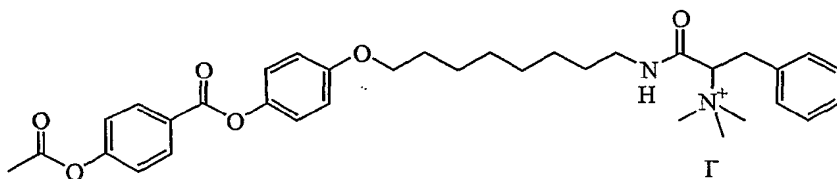
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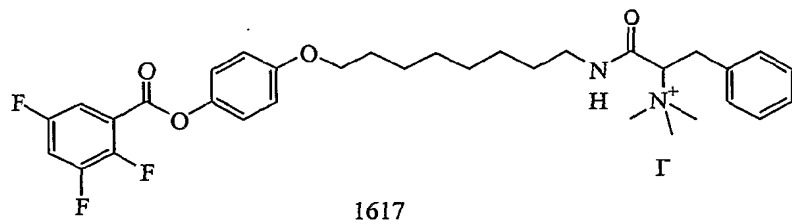


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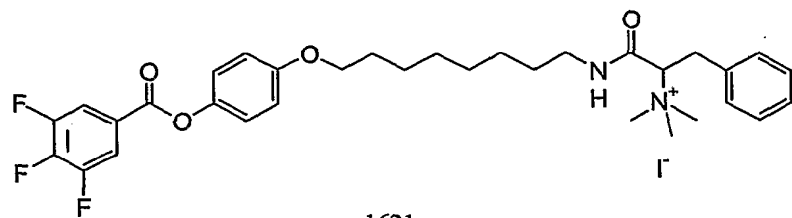
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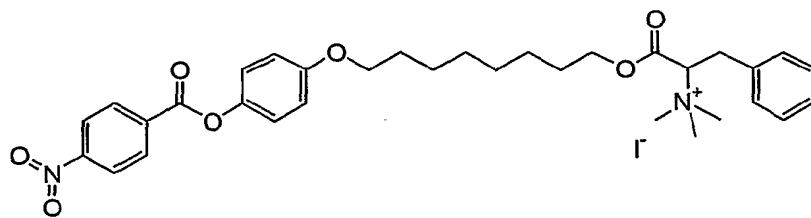


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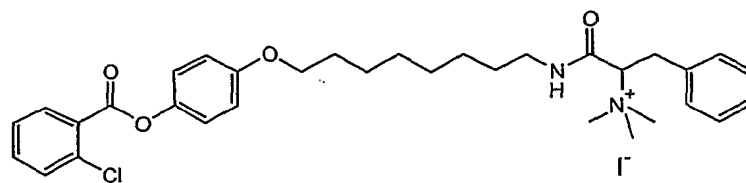


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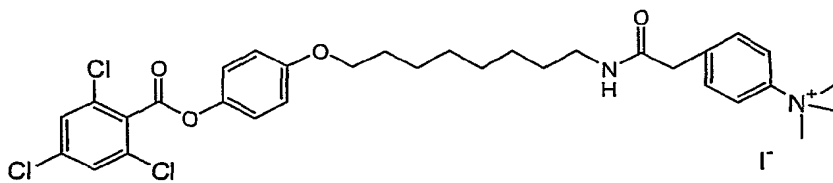
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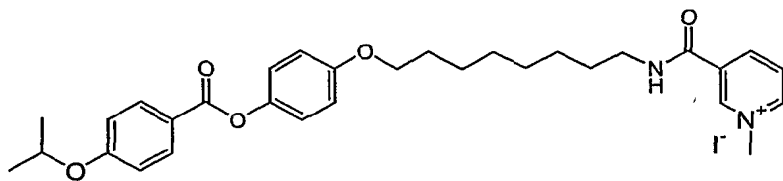
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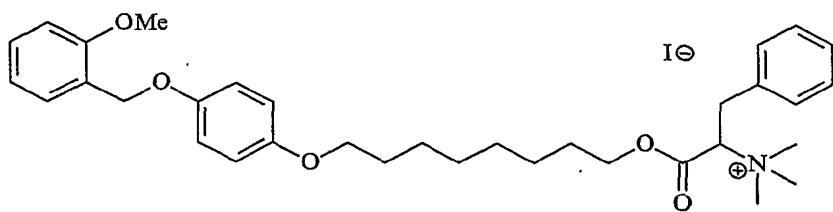


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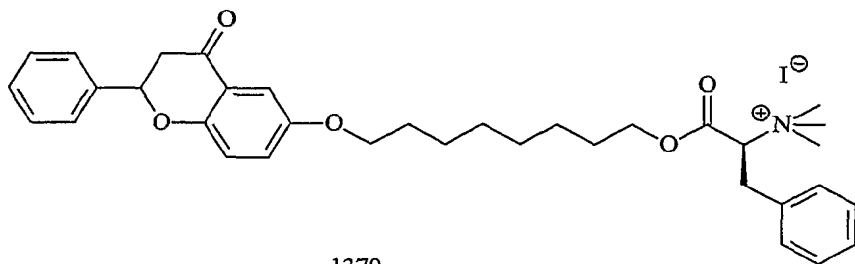


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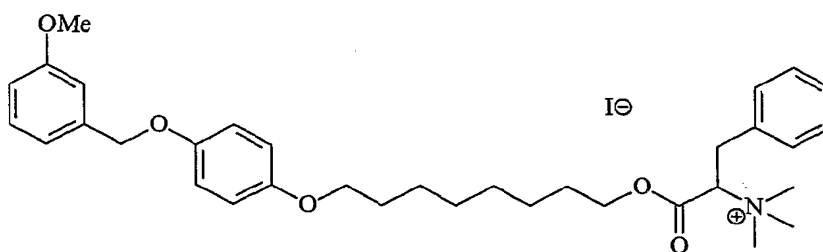
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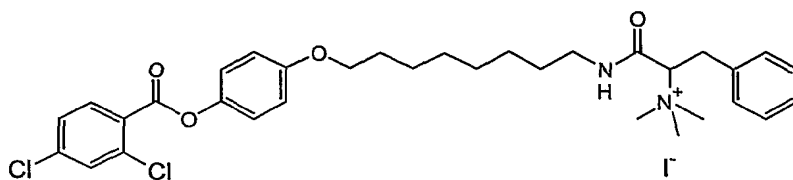
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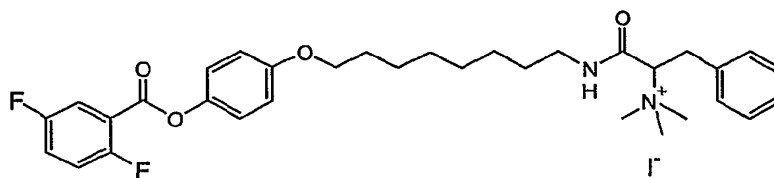
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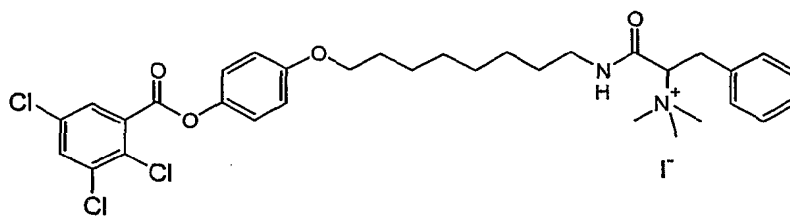
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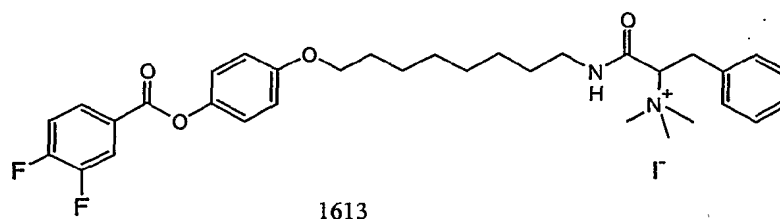
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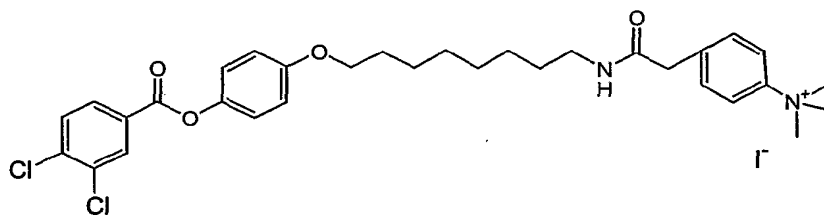
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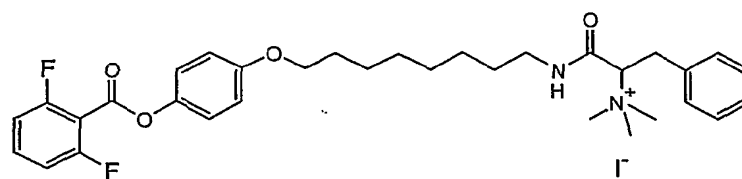
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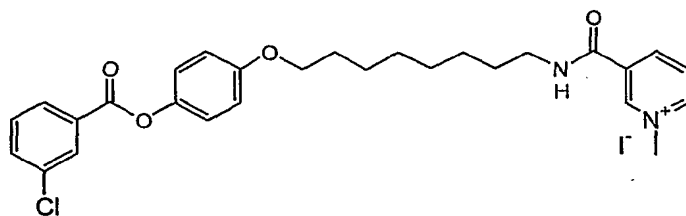


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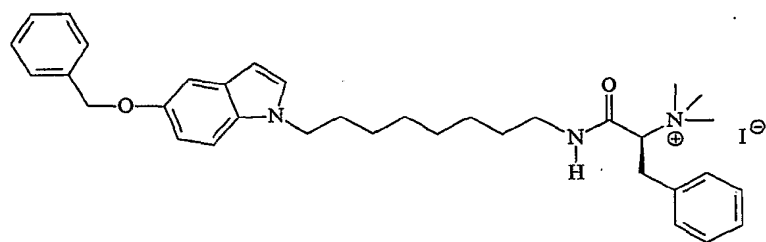
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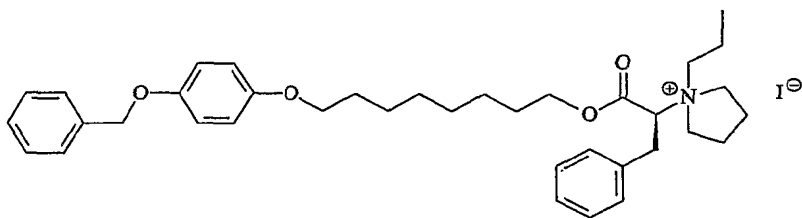


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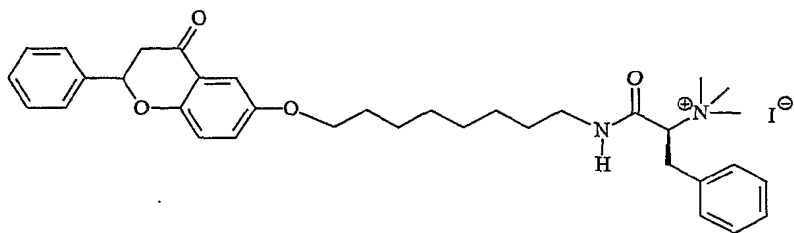


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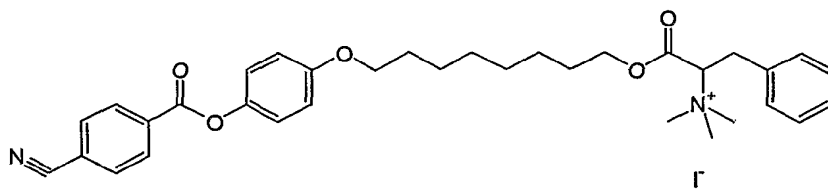
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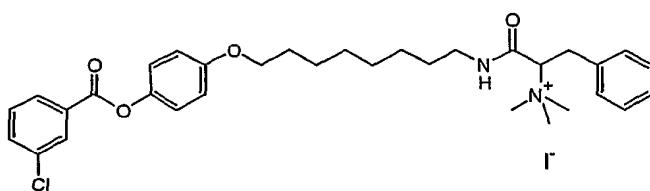


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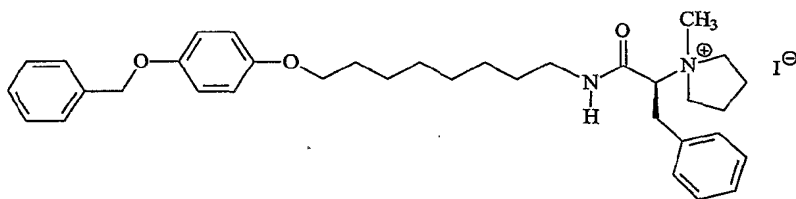
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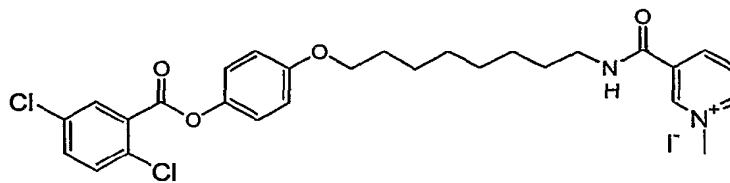
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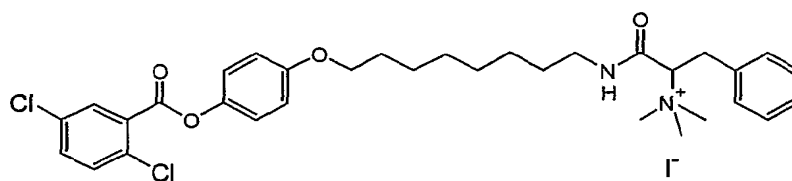


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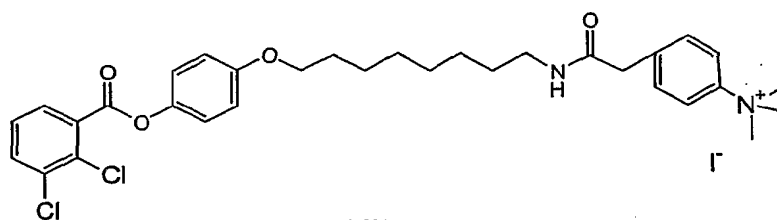


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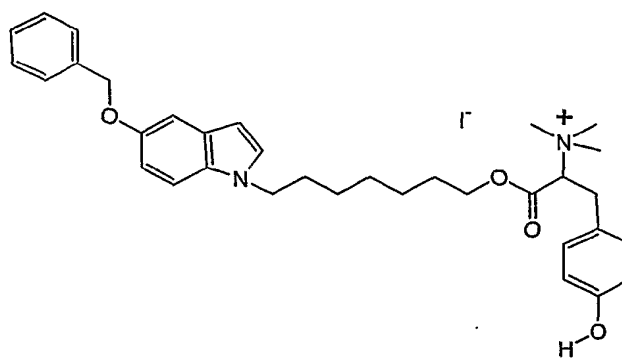


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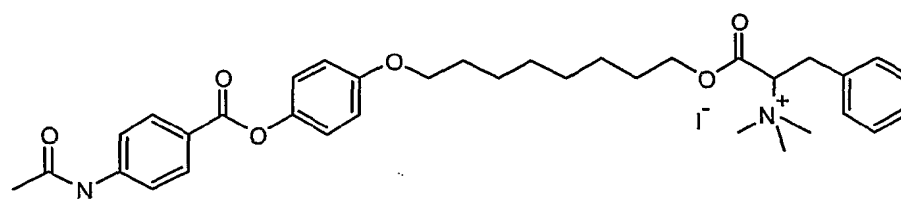


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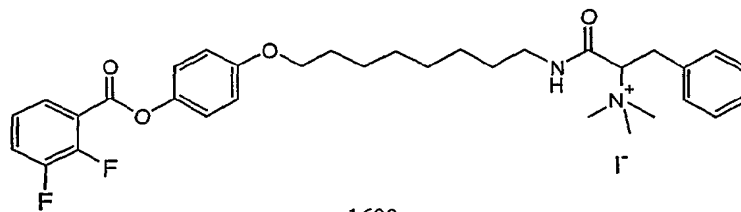
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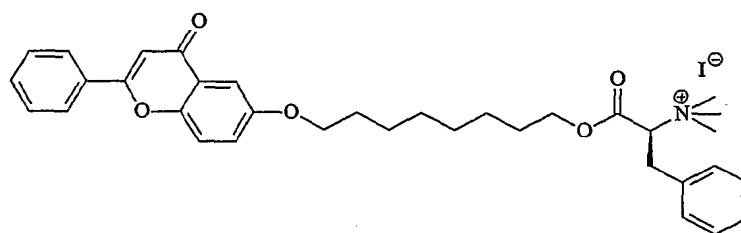
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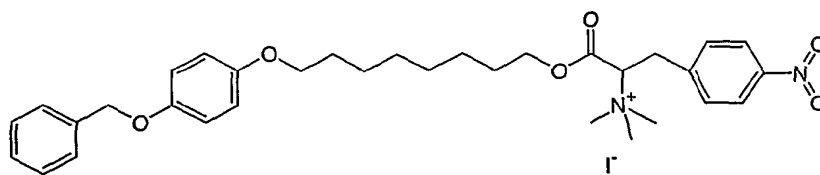


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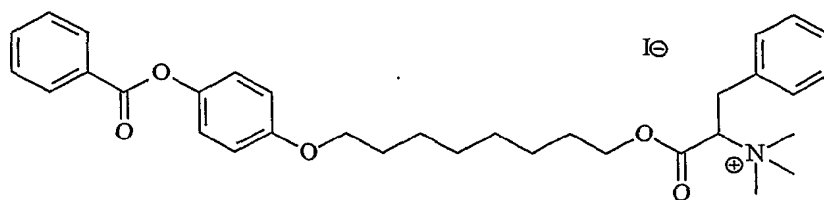


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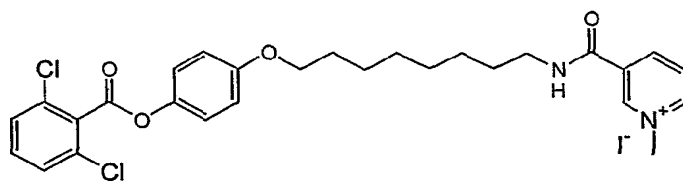
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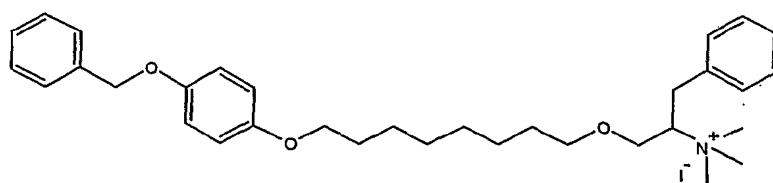
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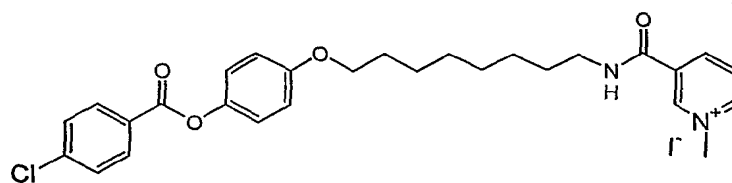


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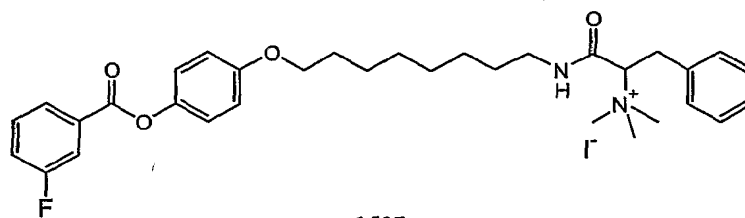
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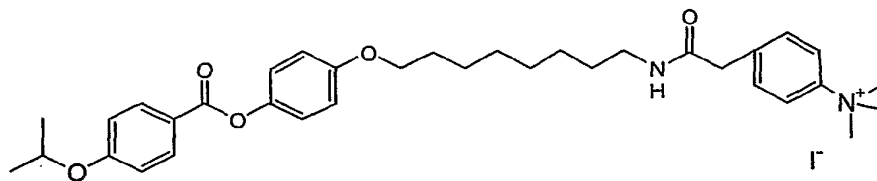
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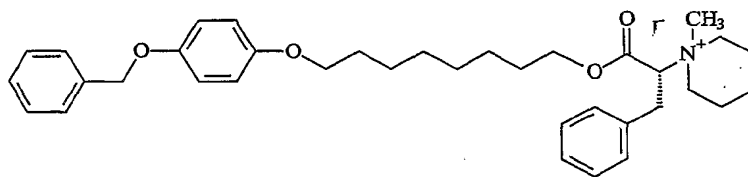


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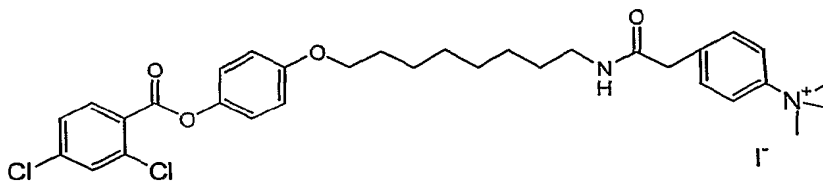


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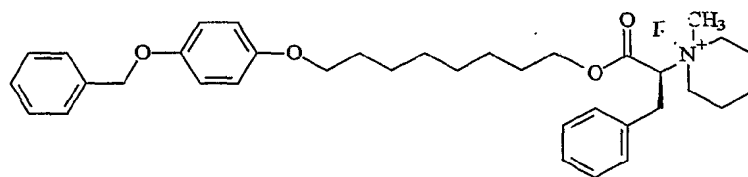


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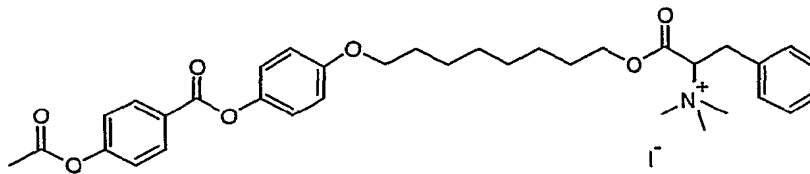


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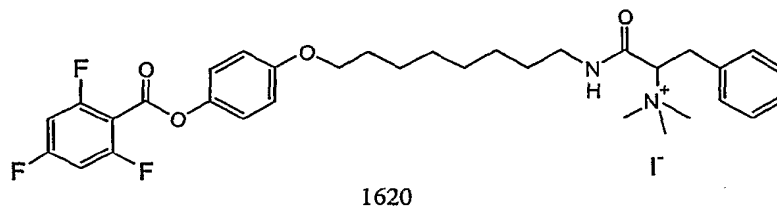
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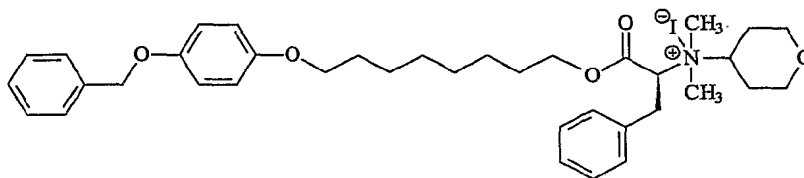
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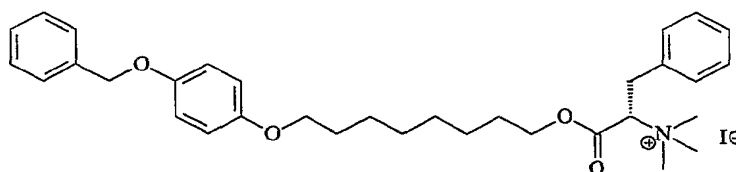


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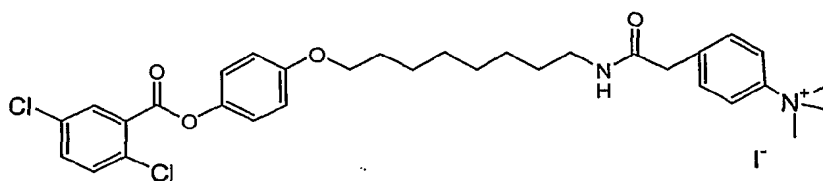


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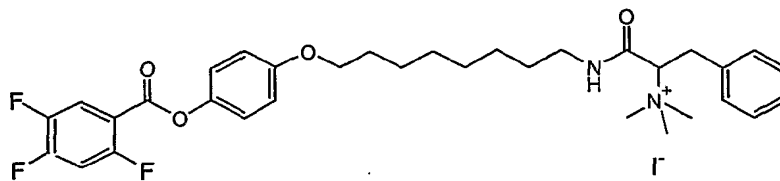
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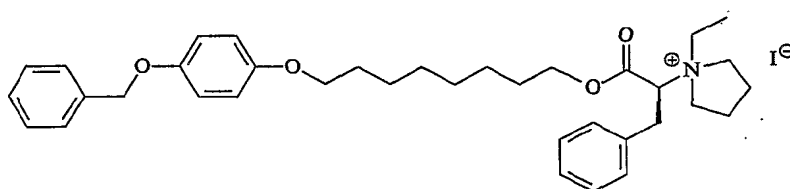
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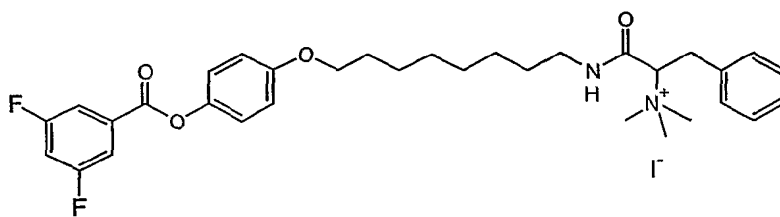


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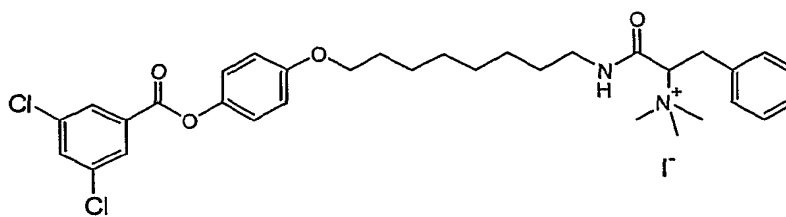


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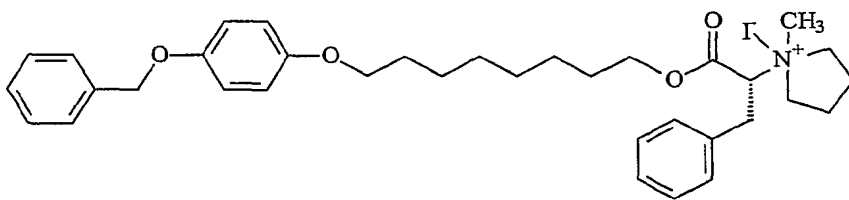
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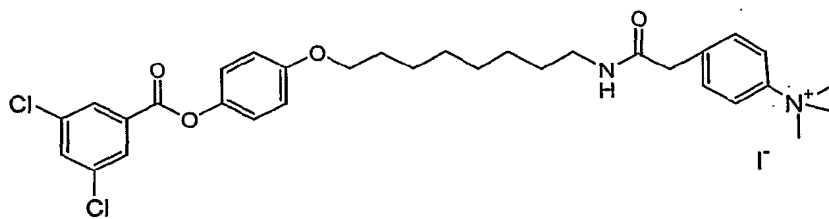
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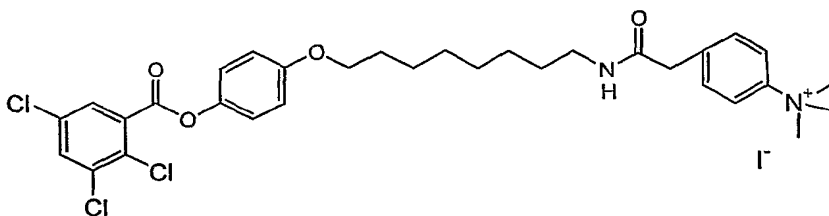


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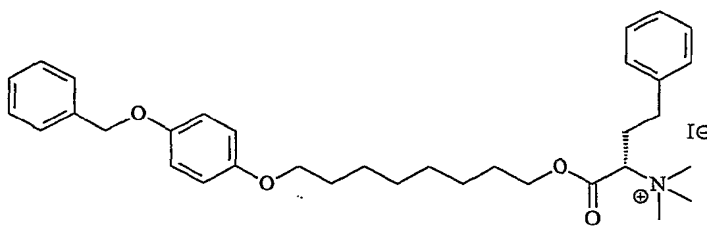


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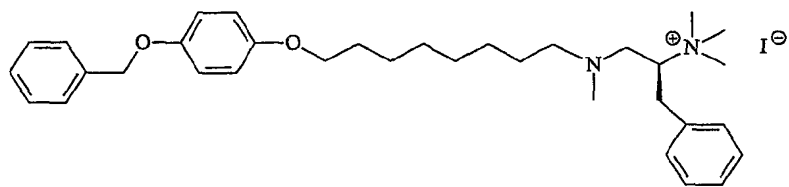
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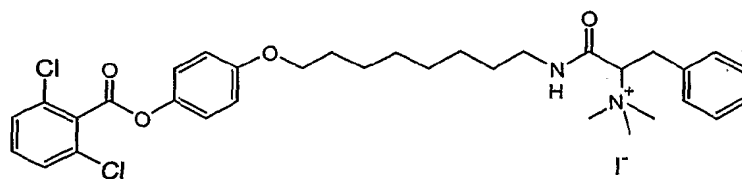
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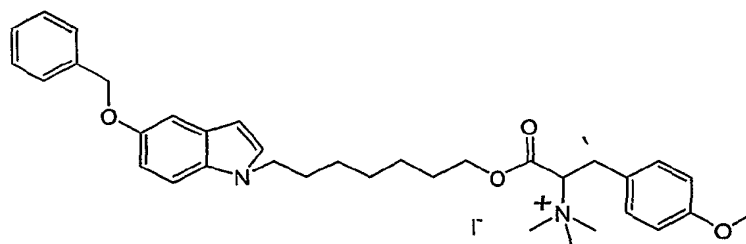


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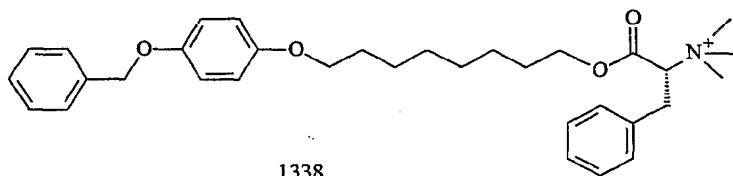


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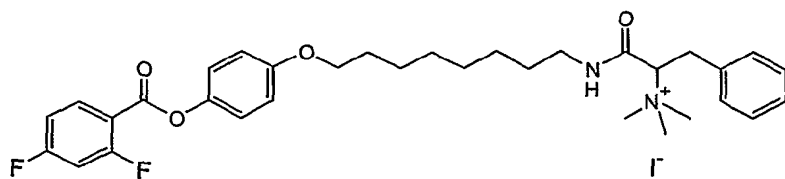
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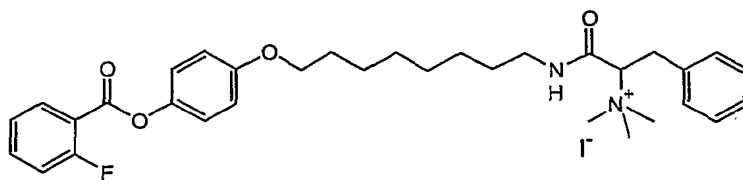
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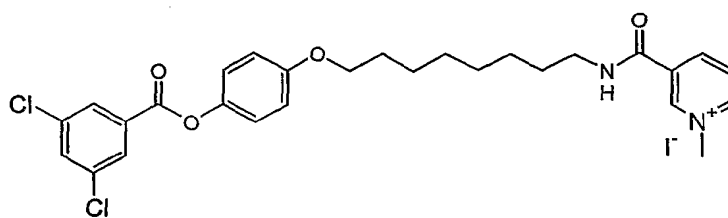
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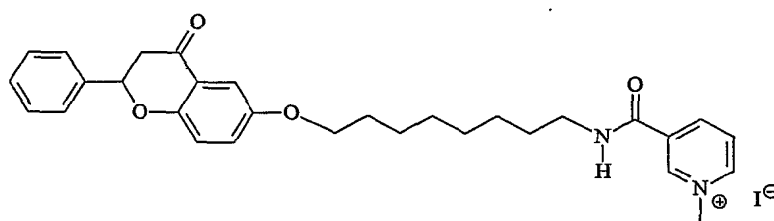
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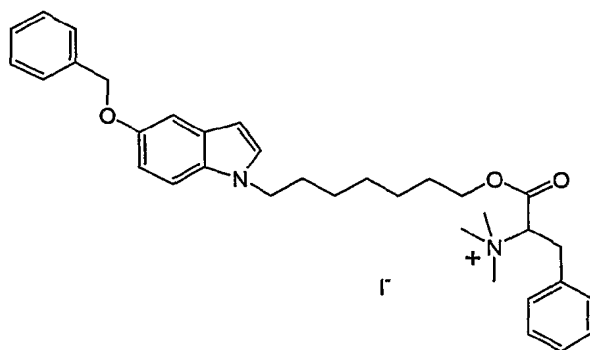


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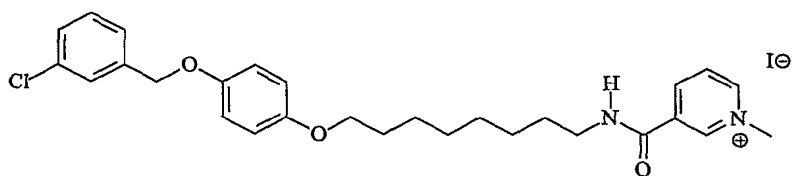
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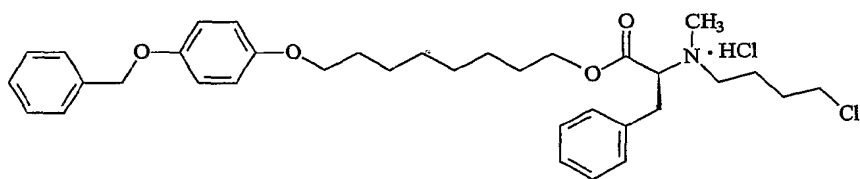


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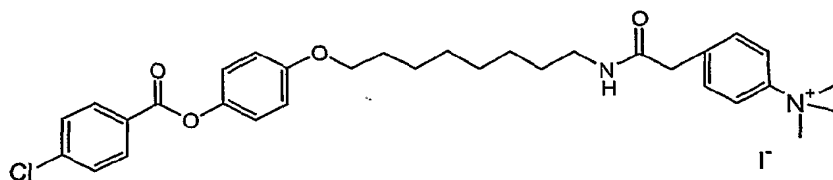


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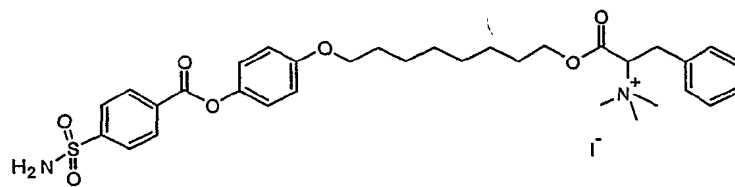
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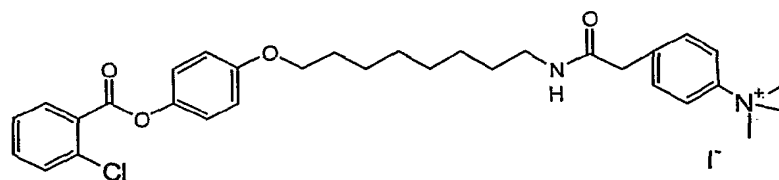
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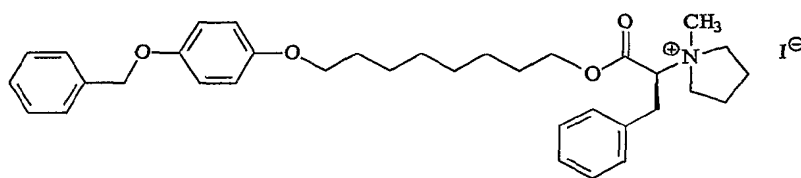


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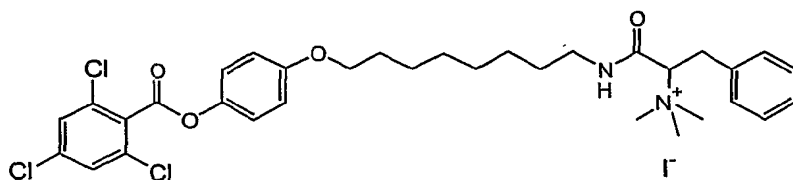


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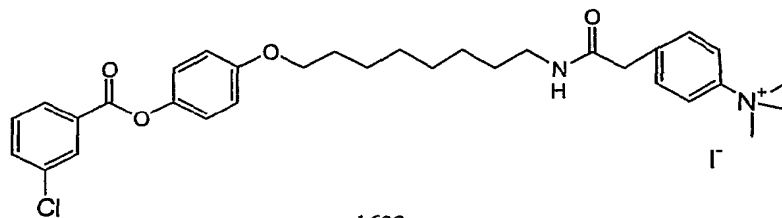


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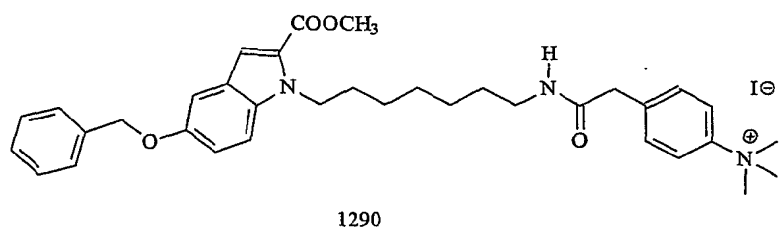
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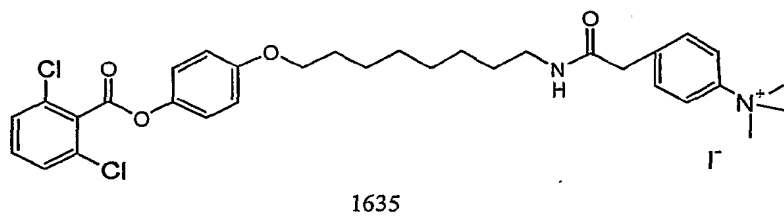
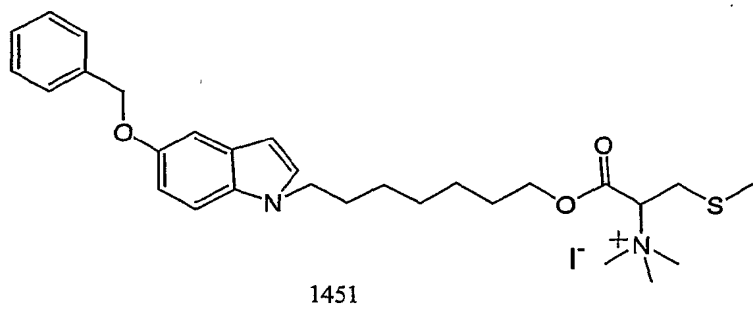


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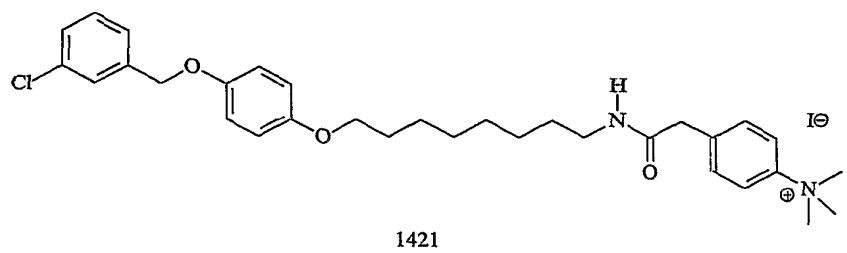
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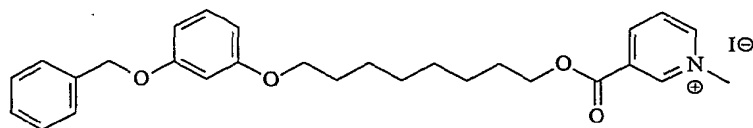


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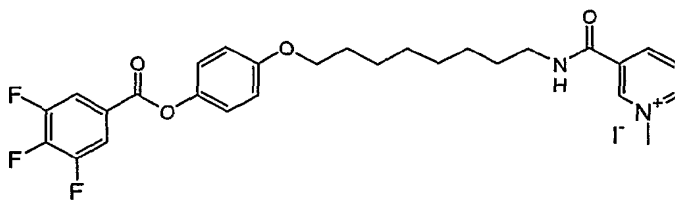
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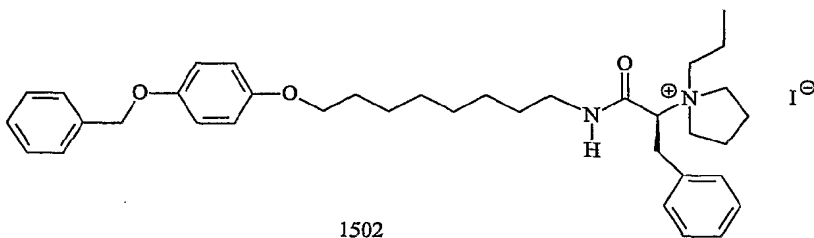
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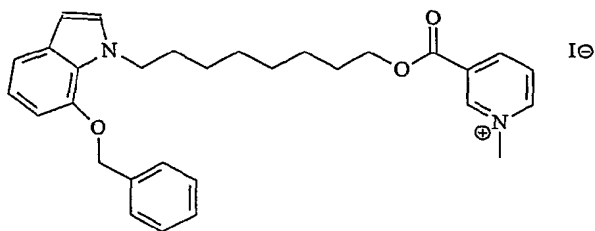
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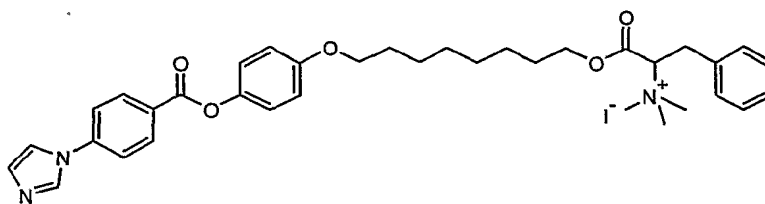
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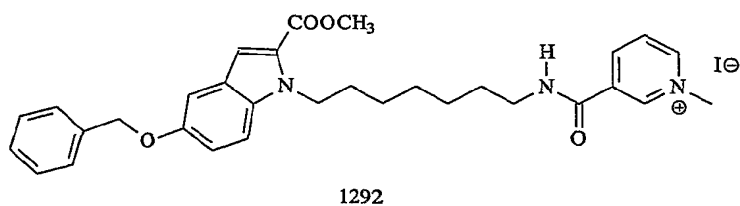
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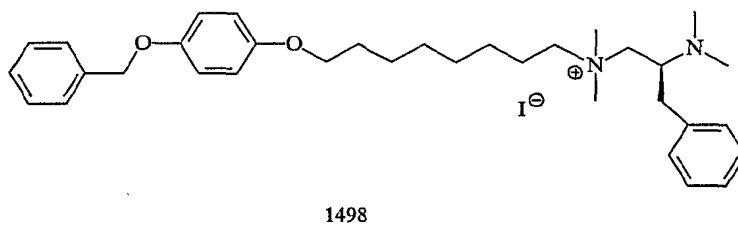
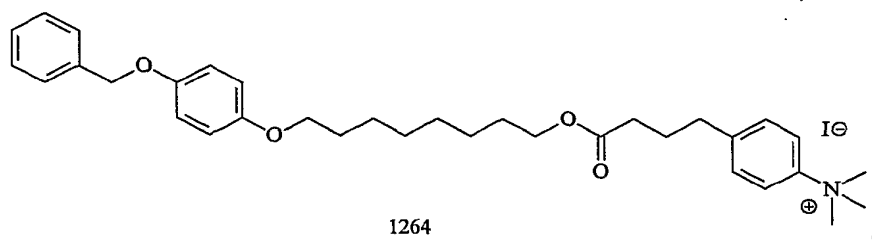
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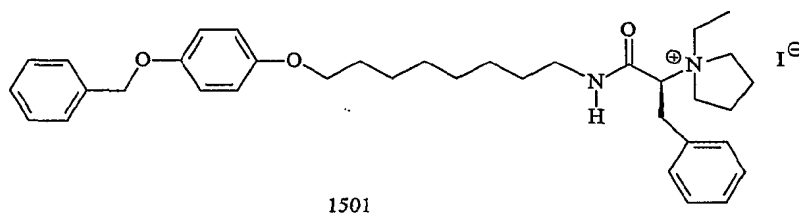
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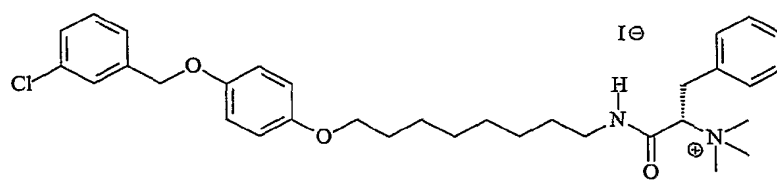


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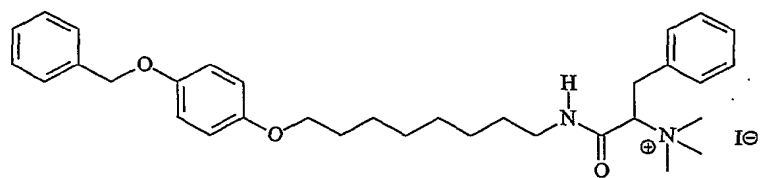


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176

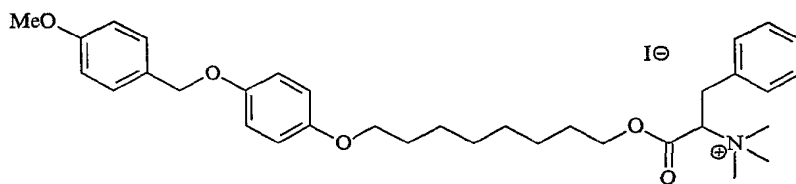


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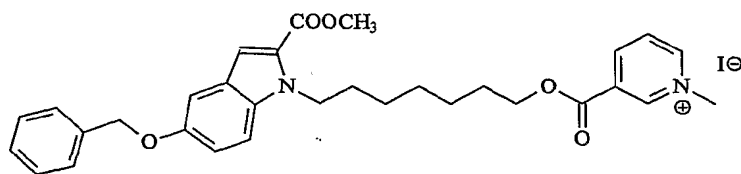
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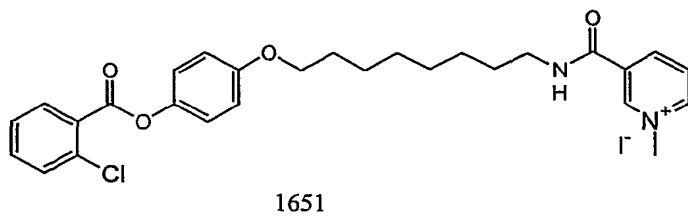
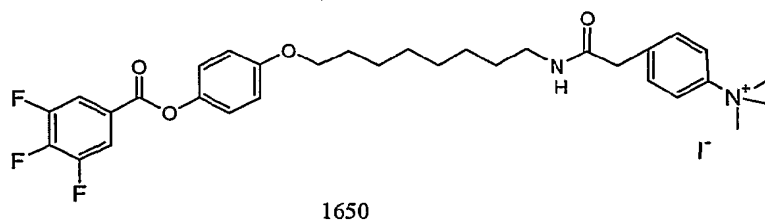
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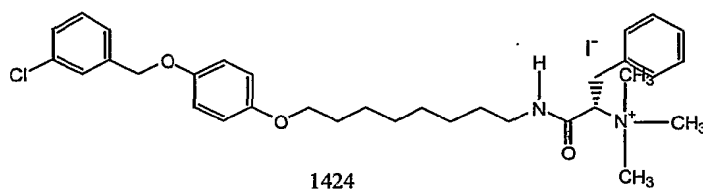
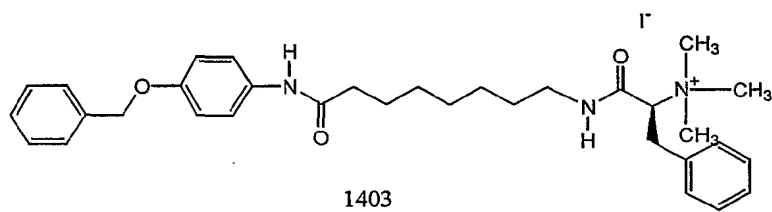


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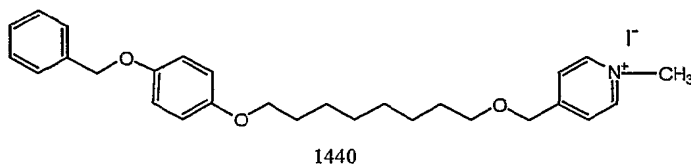
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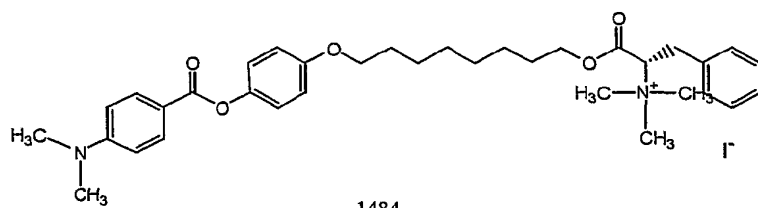


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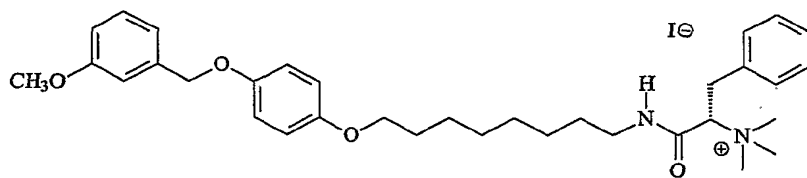


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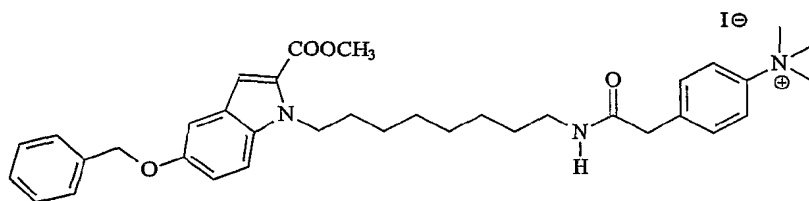


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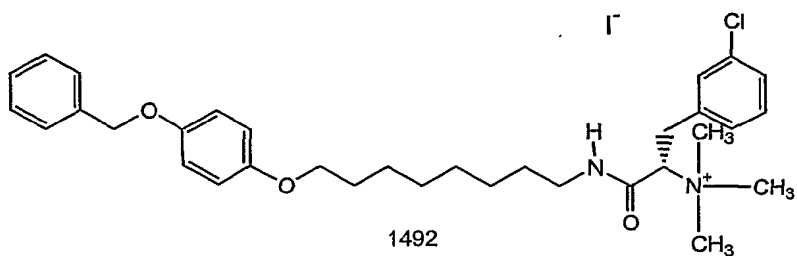


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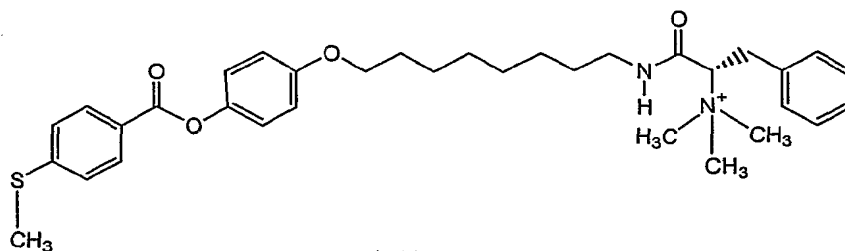


1492

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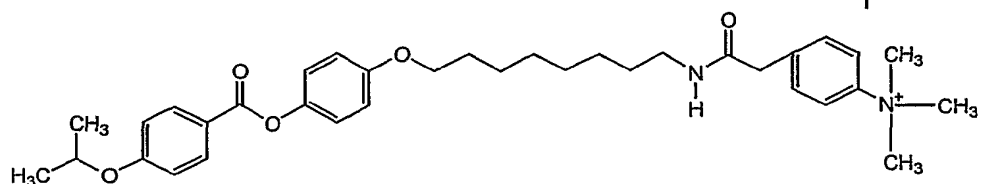
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179

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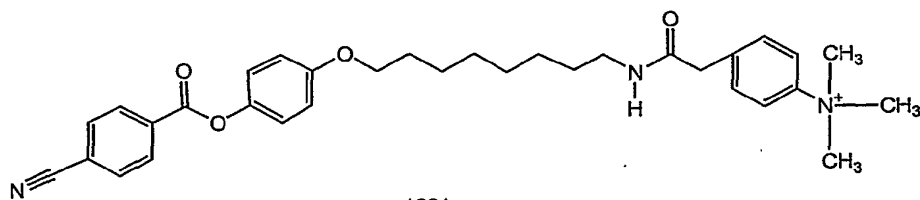
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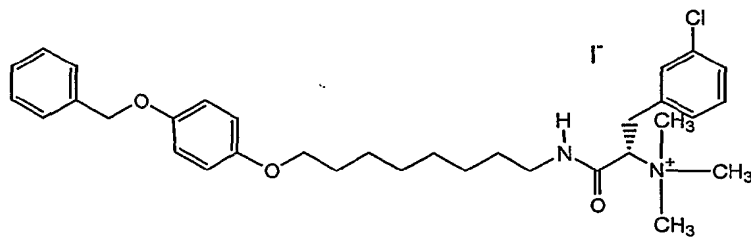
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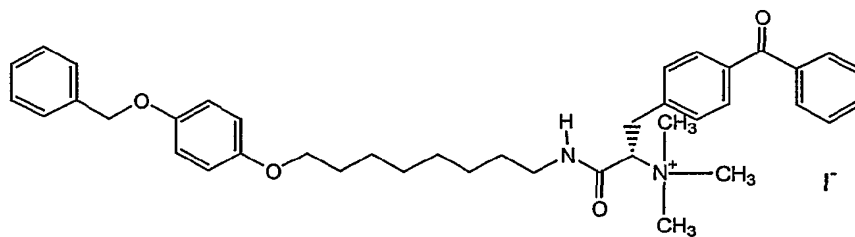
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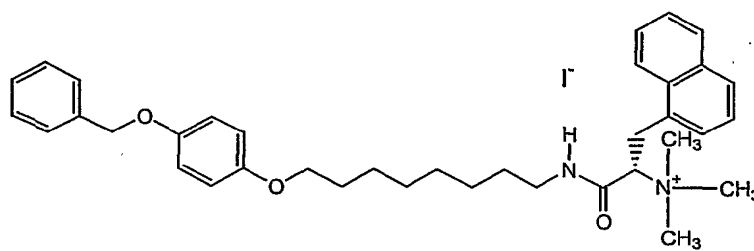
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180



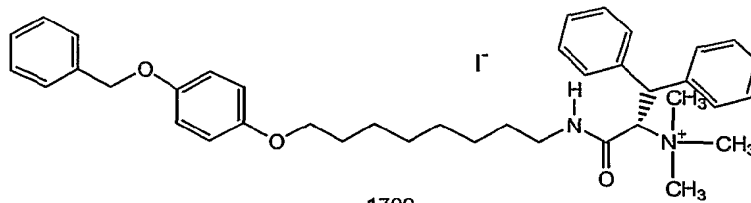
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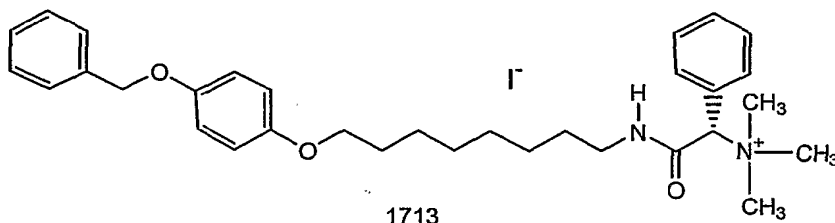
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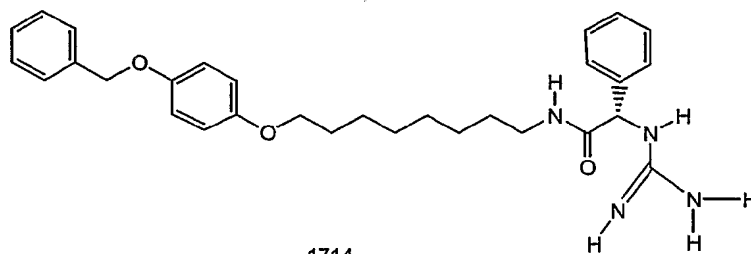
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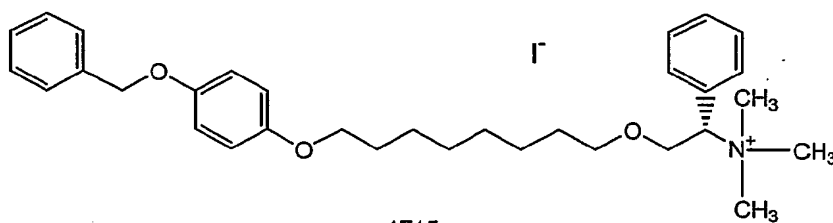
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181



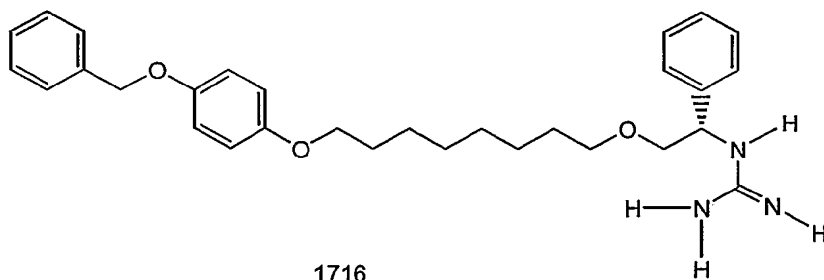
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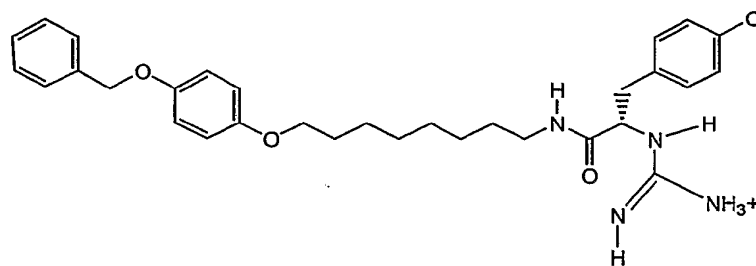


1715

10



1716



1722

15

1/3

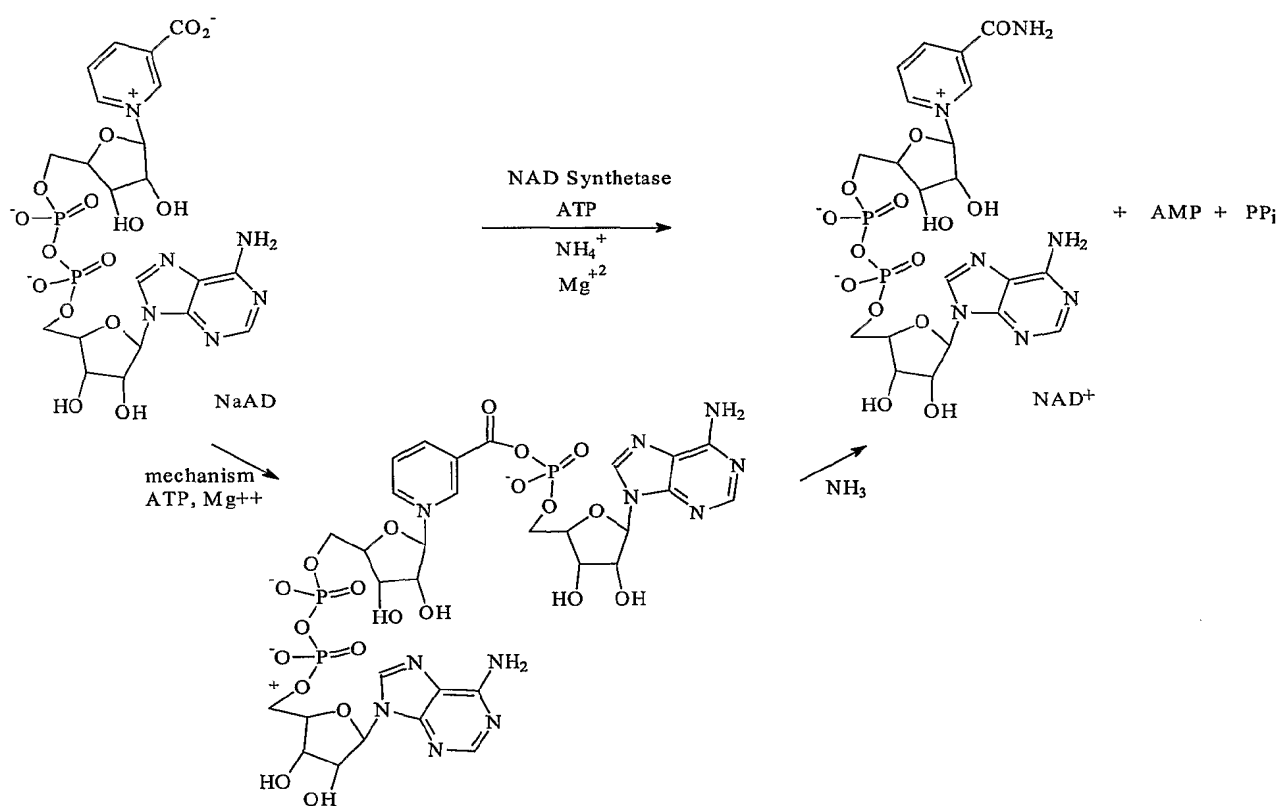


Fig. 1

2/3

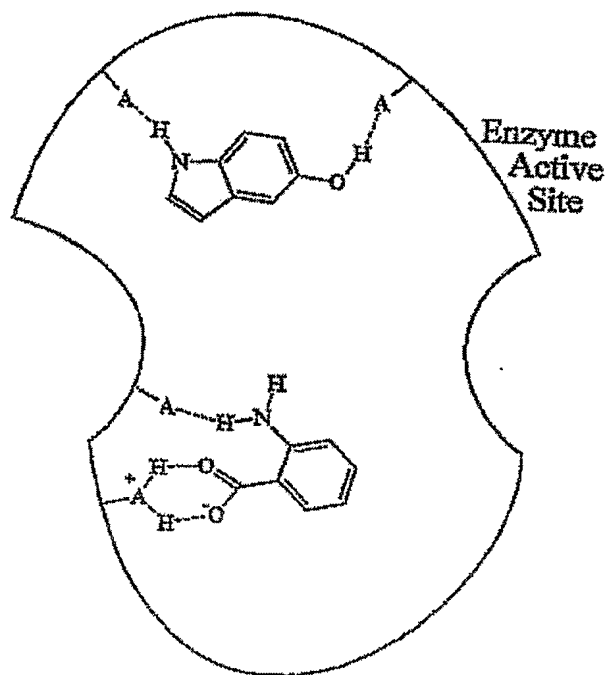


Fig. 2

3/3

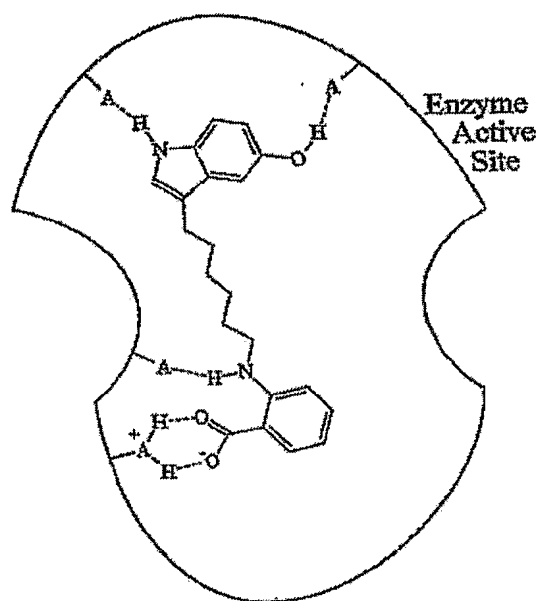


Fig. 3